UNIVERSITAT DE BARCELONA

Mapping apathy in Huntington's disease: a combined dimensional neuroimaging approach

Audrey E. De Paepe

Mapping apathy in Huntington's disease: a combined dimensional neuroimaging approach

Audrey E. De Paepe

Bellvitge Biomedical Research Institute, Neurosciences

Cognition and Brain Plasticity Unit

Submitted for the Degree of Doctor of Philosophy

PhD Program in Biomedicine

(Neurosciences)

University of Barcelona

Supervisor:

Dr. Estela Camara Mancha

Tutor:

Dr. Ruth de Diego Balaguer

Acknowledgements

As many of those who know me will appreciate, this Doctoral Thesis marks the capstone of more than seven years spent with the Cognition & Brain Plasticity Unit, our beloved 'Brainvitge'. As I was considering enrolling in the PhD program, one doctor advised me that, "At the very least, a PhD will teach you perseverance." While this is very much true, embarking on this academic odyssey also reinforced the lesson that going further means going together. In other words, many people formed a part of this journey. These people cheered me on, lent strong shoulders for me to stand on, and taught me lessons in statistics as much as in life, reminding me to stop and smell the flowers along the way.

For this, I would like to extend gratitude to many individuals, not all of whom I can name in these pages. First and foremost, thank you to my supervisor, Dr. Estela Càmara Mancha. From the very beginning, it was you, Estela, who recognized my eagerness to learn and introduced me to the world of neuroimaging. Later, it was Estela who planted the seed of possibility which prompted me to formally matriculate in the PhD program. She has been a bedrock of support for the sprouts that have sprung from this endeavor, carefully tending to each project and teaching me creativity, resourcefulness, patience, and perspective. Beyond this, Estela has served as a sort of mother to me while living abroad, bringing homemade panellets to the lab during la Castanyada and even inviting me to spend Christmas with her family when I couldn't make it home over the holidays.

Thank you also to my tutor, Dr. Ruth de Diego Balaguer, who graciously received me for my initial summer internship and tour of Brainvitge during my first of many stays in Barcelona. Your comments on each manuscript draft and cover letter provided vision and depth and helped me communicate clearly and think innovatively. Additionally, I am grateful to each of the other principal investigators of the Unit who have been there since the start, who organized seminars and offered ánimos: Lluís Fuentemilla Garriga, Josep Marco-Pallarés, and Antoni Rodríguez-Fornells.

Thank you also to the other members of Brainvitge. It has been so meaningful to partake in the creative and physical space of our Modular. This encompasses, without a doubt, those who constitute the soul of this ship: Joan Rodríguez and David "QQ" Cucurell. In addition, I have been especially blessed to share the workspace in Room 1.4B, with its rotating cast of incredibly warm and immensely intelligent individuals, who also happen to know how to throw down at a winter party or welcome picnic: Anna G., Alicia, Carles, Yemila, Francesco, Berta, Ignasi, Javiera, Marta S., Vicky, Bianca, Ieva, Brian, Montse, Helena P., Elena K., Maria D., Natasha, Matthew, Xiongbo, and Ludovico. To many of the other members of Brainvitge who have come, gone, and (if we are lucky) returned, it has been an honor and delight to watch many of you grow from interns, Master's

students, and collaborators to PhD candidates, post-docs, PIs, and leaders in other pursuits: Alberto, Paula, Jacint, Emma, Marc S., Joan T., Marc D., Ana Lucía, Eylül, Laura Fornari, Alexis, Ernest, Josué, Alexandros, Dani, Marta M., Gemma, Claudia, Guillem, Jennifer, Patricia, Neus, Alba, Lucía, Xavi, Toni C., Helena A., Mireia, Mafe, Víctor, Ana Z., Xim, Adrià, Marc B., Laura Ferreri, Ane, Pol, Clem, Anna M., Noèlia, Jeison, Joan O., Anira, Pablo, Pau, and Clara.

A special thanks to the co-authors of the projects that formulate and extend beyond this Doctoral Thesis, as well as the colleagues who offered an insightful tool or angle for a paper or peer review. I also have great appreciation for the many people I crossed paths with at conferences and workshops along the way. You each have left your mark with your inquisitive questions and feedback, while sharing laughter and life experiences. My deepest gratitude also goes, of course, to the patients and their families who made this work possible through their participation as we work to better understand this disease.

I would be remiss to not give extra recognition to a select handful of teammates who have taught me much about what it means to be both a rigorous scientist and a heartfelt friend. Over the years, we have shared trips to the Costa Brava and the Costa Daurada, with many homemade dinners, birthday celebrations, calçotades, and glasses of vermut in between: Asia Sierpowska, Paula Lopez-Gamundi, Marta Silva, Vicky Bikou, Bianca Franzoia, Emma Segura, and Laura Fornari.

Of course, this work would not have been possible without my closest connections outside of the science circles, who sustained me with reminders that there is indeed a world beyond the piles of papers to be pored over and revisions to resubmit. We have shared many phone calls, afternoons on the terraza, sports sessions, lecture halls and hospital halls, and mountain adventures over the years and even across continents. You know who you are. ♡

Lastly, of course, to those who know me best, whether over the course of this past year or since the day I was born: my life partner and my family, my Michael, Marie, Lauren, Kate, and John. Thank you for providing a steady space for my first steps and my most recent achievements, for offering a shoulder on which to drift asleep or to dry my tears, and for nourishing me with warm meals and boundless love. You are very literally the reason I exist, and you continue to be the reason I dance freely in the party that is life.

Table of Contents

List of Abbreviations *11*

Abstract *12*

Resumen *15*

Chapter 1 Introduction *19*

1.1 An Overview of Apathy **21**

1.2 Apathy: A Complex Multidimensional Construct **23**

1.2.1 Definition of Apathy 23

1.2.2 Apathy Dimensions 26

1.2.3 Interim Summary I 29

1.3 Operationalization of Apathy **30**

1.3.1 Diagnostic Criteria of Apathy 30

1.3.2 Quantifying Apathy 34

1.3.3 Interim Summary II 38

1.4 Apathy in the Context of Other Clinical Features **39**

1.4.1 Apathy and Depression 39

1.4.2 Apathy and Cognition 40

1.5 Neural Underpinnings of Apathy **41**

1.5.1 Networks of Global Apathy 41

1.5.2 Networks of Apathy Dimensions 44

1.5.3 Interim Summary III 48

1.6 Huntington's Disease **48**

1.6.1 An Overview of Huntington's Disease 48

1.6.2 Apathy in Huntington's Disease 52

1.6.3 Structural Neural Correlates of Apathy in Huntington's Disease 56

1.6.4 Interim Summary IV 63

Chapter 2 Research Aims *65*

Chapter 3 Methods *73*

3.1 Participants **75**

3.2 Clinical Evaluation **76**

3.2.1 Neuropsychiatric Assessments 76

3.2.2 Additional Huntington's Disease Clinical Assessments 77

3.3 MRI Acquisition and Processing 77
3.3.1 MRI Acquisition 77
3.3.2 Pre-Processing of T1-Weighted Data (Gray Matter Volume) 78
3.3.3 Pre-Processing of DTI Data (White Matter Microstructure) 79
3.4 Data Analyses 80
3.4.1 Psychometric Properties and Dimensionality of LARS-s 80
3.4.2 VBM of T1-Weighted Images 80
3.4.3 Tractography Dissections of DTI Data 81
3.4.4 Generalized Linear Mixed-Effects Models 81
3.4.5 Disease Trajectories Clustering Analysis 82
Chapter 4 Results: Study 1 84
4.1 Background 86
4.2 Study Design 89
4.2.1 Participants 89
4.2.2 Clinical Evaluation 90
4.2.3 Neuropsychiatric Assessment 91
4.2.4 MRI Data Acquisition 92
4.2.5 Diffusion-Weighted MRI Tractography Analysis 92
4.2.6 Statistical Analyses 94
4.3 Results 95
4.3.1 Behavioral Results 95
4.3.2 Differences in Structural Connectivity for Huntington's Disease Patients and Controls 98
4.3.3 Association Between Structural Connectivity and Apathy Domains 99
4.4 Interpretation 101
Chapter 5 Results: Study 2 107
5.1 Background 110
5.2 Study Design 111
5.2.1 Participants 111
5.2.2 Clinical evaluation 113
5.2.3 MRI Acquisition and Processing 114
5.2.4 Data analysis 114
5.2.4.1 Sociodemographic and Clinical Data 114
5.3 Results 118
5.3.1 Sociodemographic and Clinical Data 118

5.3.2 VBM Results 120
5.3.3 Generalized Linear Mixed-Effects Models 122
5.4 Interpretation 126
5.5 Supplemental Information 131
Chapter 6 Results: Study 3 133
6.1 Background 136
6.2 Study Design 138
6.2.1 Participants 138
6.2.2 Clinical Evaluation 139
6.2.3 MRI Acquisition and Processing 140
6.2.4 Data Analysis 141
6.3 Results 142
6.3.1 Psychometric Properties and Dimensionality of LARS-s 142
6.3.2 Clinical Disease Progression Markers 144
6.3.3 VBM Results 144
6.4 Interpretation 149
Chapter 7 Results: Study 4 155
7.1 Background 158
7.2 Study Design 160
7.2.1 Participants 160
7.2.2 Disease Trajectories Clustering Analysis 161
7.2.3 Statistical Analyses 165
7.3 Results 166
7.3.1 Shared Psychiatric Trajectories 166
7.3.2 Group Differences in Psychiatric Trajectories 168
7.4 Interpretation 171
Chapter 8 Discussion 180
8.1 Summary of Results 183
8.2 Apathy is Prevalent and Progressive in Huntington's Disease 186
8.3 Multidimensional Apathy as a Construct 187
8.3.1 Apathy Profiles in Huntington's Disease 187
8.3.2 Apathy Profiles in Other Neurodegenerative Disorders 189

8.3.3 Integrating Frameworks for Multidimensional Apathy 191

8.4 Progress in the Operationalization of Apathy 196

8.4.1 Psychometrics of the Short-Lille Apathy Rating Scale 197

8.4.2 Apathy Tasks: Potential for Objective Measurement 197

8.5 Neural Correlates of Apathy Dimensions 200

8.5.1 Cognitive Apathy 201

8.5.2 Auto-Activation Deficit 204

8.5.3 Emotional Apathy 206

8.5.4 Implications of Dimensional Apathy Networks 208

8.6 Longitudinal Psychiatric Profiles in Huntington's Disease 209

8.6.1 Apathy, Depression, and Executive Functions 210

8.6.2 Apathy in Relation to Other Psychiatric Disturbances 212

8.6.3 A Promising Perspective: Interrelating Psychiatric Features Through Disease Profiles 215

8.7 General Limitations and Considerations 217

8.7.1 Apathy Scales 217

8.7.2 Clinically Relevant Apathy 218

8.7.3 Structural Neuroimaging 219

8.7.4 Clinical Profiles 220

8.8 Future Directions 221

8.8.1 Operationalizaing Apathy 221

8.8.2 Neurocircuitry of Apathy 223

8.8.3 Clustering Disease Profiles 224

Chapter 9 Conclusions 227

Chapter 10 References 231

List of Tables 307

List of Figures 308

List of Abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann area
CAG	Cytosine-adenine-guanine polyglutamine
CAP	CAG-age product
dACC	Dorsal anterior cingulate cortex
dlPFC	Dorsolateral prefrontal cortex
dlPFC-cn	Dorsolateral prefrontal cortex to caudate nucleus tract
dmPFC	dorsomedial prefrontal cortex
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FST	Frontostriatal tract connecting caudate to preSMA/SMA
GM	Gray matter
GMV	Gray matter volume
HD	Huntington's disease
LARS(-s)	(Short-)Lille Apathy Rating Scale
MCC	Middle cingulate cortex
MD	Mean diffusivity
MNI	Montreal Neurological Institute coordinates
OFC	Orbitofrontal cortex
PBA(-s)	(Short-)Problem Behaviors Assessment
PreSMA	Presupplementary motor area
ROI(s)	Region(s)-of-interest
SMA	Supplementary motor area
TFC	Total Functional Capacity
TIV	Total intracranial volume
UF	Uncinate fasciculus
UHDRS	Unified Huntington's Disease Rating Scale
UHDRS-cogscore	UHDRS total cognitive score
UHDRS-TMS	UHDRS total motor score
VBM	Voxel-based morphometry
WM	White matter

Abstract

What would it feel like to not feel? To go through life with an 'empty mind', unable to generate thoughts, plans, actions, or the motivation to carry out these processes? What would it be like to be defined by what you lack? These notions fall in line with the clinical syndrome of apathy: *a-* (without) *-pathos* (feeling). More recently, apathy has been defined as a reduction in goal-directed behavior and motivation. The proposed etiology of apathy is multidimensional, signifying that it can stem from deficits in self-activation, emotional affect, and the cognitive faculties required to plan and manage goals. However, the precise neurobiological mechanisms underlying each apathy dimension remain largely unknown, resulting in a dearth of validated treatment, despite its far-reaching negative impact.

While apathy can occur in the general population, it is much more prevalent in those suffering from neurodegenerative disease, including Huntington's disease. Due to its genetic etiology, it is possible to identify Huntington's disease mutation carriers through predictive testing prior to symptom onset. This renders Huntington's disease a suitable model for the study of neurodegeneration. Despite being diagnosed by motor onset, cognitive decline and psychiatric disturbances such as apathy are prevalent and can manifest years prior. Meanwhile, apathy is the only psychiatric feature that has consistently been shown to track disease progression. As such, the overarching aim of this Doctoral Thesis was to describe apathy as a multidimensional construct in Huntington's disease, while investigating its structural neural underpinnings through MRI as well as its longitudinal relationship with associated psychiatric features of the disease.

First, **Study 1** provided evidence that the short-Lille Apathy Rating Scale could quantify three apathy subdimensions in Huntington's disease in line with the triadic model of apathy. These dimensions subsume cognitive, auto-activation, and emotional apathy. Patients with greater severity in cognitive and auto-activation apathy demonstrated decreased white matter microstructural connectivity in specific frontostriatal tracts. Overall, these findings underscored that white matter dysfunction may contribute to the

heterogeneous nature of apathy in Huntington's disease, with implications for treatment selection.

Next, **Study 2** highlighted that individual differences in global apathy progression in Huntington's disease may be explained by variability in brain atrophy in the right middle cingulate cortex, an area implicated in action-initiation. Moreover, initial vulnerabilities in this region predicted those individuals who would later develop more severe and worsening apathy over time. These results were specific to apathy; neither depression nor cognitive scores were related with volume loss in this region. As a whole, these results evince that specific regional vulnerabilities may facilitate the prediction of an apathetic profile in HD, permitting targeted, time-sensitive interventions.

Returning to the study of multidimensional apathy, **Study 3** demonstrated that the short-Lille Apathy Rating Scale exhibited satisfactory reliability and clinical validity in Huntington's disease and a three-dimensional factor structure in line with the triadic model of apathy. Neurobiologically, apathy profiles in Huntington's disease were underpinned by reduced gray matter volume in nodes within functionally diverse and large-scale motor, cognitive, and limbic networks. Such findings promote the continued use of the short-Lille Apathy Rating Scale to comprehensively characterize apathy in neurological populations in clinical practice.

Finally, **Study 4** utilized a novel machine-learning approach to stratify Huntington's disease patients into unique longitudinal psychiatric trajectories. Two main psychiatric signatures were revealed, the first defined by a pattern of increasing irritability and no depression, and the second by rise-and-fall depression and no irritability. Interestingly, both signatures consisted of both premanifest and manifest Huntington's disease individuals. Notably, the severity of apathy and perseveration/obsessive-compulsiveness were increased at clinically relevant levels in both longitudinal profiles. This work opens doors for patient stratification leveraging real-world data with the potential to enhance prognostic indicators and therapeutics.

Collectively, the four studies presented in this Doctoral Thesis exemplify crucial insights regarding the underlying neural basis and progression profile of apathy in Huntington's disease. By addressing these questions, this work advances understanding of the

pathological mechanisms of apathy, a syndrome that strips an individual of their productivity, passions, and functional independence. Ultimately, this research lays the groundwork for critically examining individual differences within a certain disease diagnosis, with promise to further personalized, precision, and preventative medicine in Huntington's disease and beyond.

Keywords: apathy profiles; Huntington's disease; structural MRI; individual differences; machine learning

Resumen

¿Qué se sentiría al no sentir? Imagínese ir por la vida con una «mente vacía», incapaz de generar pensamientos, planes, acciones o la motivación para llevarlos a cabo. ¿Cómo sería definirse por lo que le falta? Estas ideas reflejan el síndrome clínico de la apatía: *a-* (sin) - *pathos* (sentimiento). Más recientemente, la apatía se ha descrito como una reducción de la conducta orientada a objetivos y a la falta de motivación. La etiología propuesta de la apatía es multidimensional, lo que significa que puede derivarse de déficits en la autoactivación, el afecto emocional y las habilidades cognitivas necesarias para planificar y gestionar objetivos. Sin embargo, los mecanismos neurobiológicos concretos que subyacen a cada una de estas dimensiones siguen siendo en gran medida desconocidos, lo que ha limitado el desarrollo de tratamientos validados, a pesar del gran impacto negativo de la apatía en la vida de quienes la padecen.

Aunque la apatía puede presentarse en la población general, es mucho más frecuente en quienes padecen enfermedades neurodegenerativas, incluida la enfermedad de Huntington. Debido a su etiología genética, es posible identificar a los portadores de la mutación mediante pruebas predictivas, antes de que aparazcan los primeros síntomas. Esto convierte a la enfermedad de Huntington en un modelo ideal para el estudio de la neurodegeneración. A pesar de que se diagnostica por la aparición de síntomas motores, el deterioro cognitivo y los trastornos psiquiátricos, como la apatía, son prevalentes y pueden manifestarse muchos años antes. De hecho, la apatía es el único rasgo psiquiátrico que se ha demostrado que sigue la progresión de la enfermedad. Así, el objetivo general de esta Tesis Doctoral fue describir la apatía como un constructo multidimensional en la enfermedad de Huntington, mientras se investigaban sus bases neurales estructurales mediante la resonancia magnética, así como su relación longitudinal con otros síntomas psiquiátricos asociados a la enfermedad.

El **Estudio 1** proporcionó evidencia de que la Escala Breve de Calificación de la Apatía de Lille (*short-Lille Apathy Rating Scale*) permite cuantificar tres subdimensiones de la apatía en la enfermedad de Huntington, en consonancia con el modelo triádico de la apatía: la apatía cognitiva, la de auto-activación y la emocional. Se observó que los pacientes con mayor gravedad en la apatía cognitiva y de auto-activación mostraban una disminución

de la conectividad microestructural de la sustancia blanca en tractos frontoestriatales específicos. Estos hallazgos subrayan que la disfunción de la sustancia blanca contribuye a la naturaleza heterogénea de la apatía en la EH, lo que podría tener implicaciones para la selección de tratamientos.

El **Estudio 2** mostró que las diferencias individuales en la progresión de la apatía global en la enfermedad de Huntington pueden explicarse por la variabilidad en la atrofia cerebral en el córtex cingulado medio derecho, una región implicada en la iniciación de la acción. Además, las vulnerabilidades iniciales en esta región predijeron qué individuos desarrollarían una apatía más severa y que empeoraría con el tiempo. Estos resultados fueron específicos de la apatía; ni la depresión ni las puntuaciones cognitivas se relacionaron con la pérdida de volumen en esta región. En conjunto, estos resultados ponen de manifiesto que la pérdida de volumen en esta región es específica de la apatía y que identificar estas vulnerabilidades regionales específicas podría ayudar a predecir el desarrollo del perfil apático en la EH, facilitando intervenciones específicas y sensibles al tiempo.

El **Estudio 3** evidenció que la Escala Breve de Calificación de la Apatía de Lille (*short-Lille Apathy Rating Scale*) presentaba una fiabilidad y validez clínica adecuadas para la enfermedad de Huntington, con una estructura factorial tridimensional que respalda el modelo triádico de la apatía. Desde el punto de vista neurobiológico, se observó que los perfiles de apatía en la enfermedad de Huntington estaban asociados a una reducción del volumen de materia gris en nodos dentro de redes motoras, cognitivas y límbicas funcionalmente diversas y a gran escala. Estos hallazgos promueven el uso continuado de la Escala Breve de Calificación de Apatía de Lille para caracterizar de forma exhaustiva la apatía en poblaciones neurológicas en la práctica clínica.

Por último, el **Estudio 4** utilizó un novedoso enfoque de aprendizaje automático para estratificar a los pacientes con enfermedad de Huntington en trayectorias psiquiátricas longitudinales únicas. Se identificaron dos patrones principales: uno marcado por un aumento de la irritabilidad sin depresión, y otro con depresión fluctuante sin irritabilidad. Curiosamente, ambos grupos incluían individuos en fases premanifiesta y manifiesta de la enfermedad. En particular, la gravedad de la apatía y la perseveración/obsesividad-compulsividad aumentaron a niveles clínicamente relevantes en ambos perfiles

longitudinales. Este enfoque abre las puertas a la estratificación de pacientes aprovechando datos del mundo real con el potencial de mejorar los pronósticos y las intervenciones terapéuticas.

En conjunto, los cuatro estudios presentados en esta Tesis Doctoral ofrecen importantes aportaciones sobre la base neural subyacente y el perfil de progresión de la apatía en la enfermedad de Huntington. Al abordar estas cuestiones, este trabajo avanza en la comprensión de los mecanismos patológicos de la apatía, un síndrome que priva al individuo de su productividad, sus pasiones e independencia funcional. En última instancia, esta investigación sienta las bases para el examen crítico de las diferencias individuales dentro de un determinado diagnóstico de la enfermedad, con la promesa de avanzar en la medicina personalizada, de precisión y preventiva en la enfermedad de Huntington como en otros trastornos neurodegenerativos.

Palabras clave: perfiles de apatía; enfermedad de Huntington; resonancia magnética estructural; diferencias individuales; aprendizaje automático.

Chapter 1
Introduction

Chapter 1 | Introduction

1.1 An Overview of Apathy

Apathy stems from the Greek word *apatheia*: a- (without) and -pathos (feeling). In ancient Stoic philosophy, apathy was deemed a desirable state of reason overcoming emotion, leading to emotional indifference and ensuing enlightenment. Over time, however, the negative impact of apathy on oneself and others has since become apparent. As such, apathy is now regarded as pathological and, more recently, a distinct clinical syndrome that is prevalent across diagnostic categories. Presently, apathy is defined as a lack of motivation (Marin, 1991) or goal-directed behavior (R. Levy & Dubois, 2006). Nonetheless, there are many gaps in its study. In particular, the exact etiology and pathological mechanisms of apathy remain unknown, resulting in a dearth of validated treatment options. The fact that this syndrome has a deleterious effect on many lives, lacks a unified definition, and remains elusive in etiology and treatment makes apathy a relevant topic for study.

Considered a transdiagnostic construct, apathy is a prevalent psychiatric manifestation across a range of brain disorders, including neurodegenerative disease, stroke, traumatic brain injury, major depressive disorder, and schizophrenia. When examining neurodegenerative disorders, apathy is the single most prevalent neuropsychiatric sign in Huntington's disease (HD) and Alzheimer's disease, and is also routinely observed in Parkinson's disease, frontotemporal dementia, vascular dementia, and progressive supranuclear palsy (Cummings et al., 2024). Concomitantly, apathy may be a common feature in the otherwise healthy elderly. Indeed, two studies illustrated that apathy is present in 20% to 27% of non-demented elderly community-members (Ligthart et al., 2012; van der Mast et al., 2008). Even in healthy younger individuals, symptomatic apathy may occur, with debilitating consequences in daily life (Lafond-Brina & Bonnefond, 2022; Pardini et al., 2016).

No matter the population, apathy bears a significant negative impact on quality of life for both individuals suffering from apathy and their caregivers, affecting day-to-day

functioning and social life (Andrieu et al., 2016; Chase, 2011). What's more, apathy is associated with faster cognitive and functional decline (Grossi et al., 2013; Lechowski et al., 2009; Starkstein et al., 2006), greater risk of conversion from cognitively normal to mild cognitive impairment (Geda et al., 2014), a three-fold increased risk of mortality (van der Linde et al., 2017), increased caregiver burden and time (Chen et al., 2018; Haro et al., 2014), and increased cost of care (Kruse et al., 2023). Apathy can also negatively impact willingness to engage in treatment, and therefore warrants careful consideration.

Still, at present, there are no clinical guidelines or approved medications for the treatment of apathy (Azhar et al., 2022; Cummings et al., 2024). This may be attributable to the incomplete understanding of the pathological mechanisms and neural circuits that give rise to apathy. As an example, the complexity of neurotransmitters implicated in apathy is immense and include dopamine, acetylcholine, noradrenaline, serotonin, and gamma-aminobutyric acid (Ruthirakuhan et al., 2018). Simultaneously, there is a paucity of clinical trials that examine apathy as a primary outcome measure and there remain inconsistencies in its operationalization (i.e., translating abstract conceptual ideas of apathy into measurable observations). As a whole, this leads to a consequential lack of a gold standard for apathy assessment across disorders. Taken together, there is a crucial need for consensus in the definition of apathy and its dimensions, as well as the continued study of its underlying neural circuitry.

Overall, in order to pursue investigations in the neurobiological circuits of apathy, it is first necessary to outline a working definition of apathy and its triadic structure, examine the evolution of its diagnostic criteria, review how apathy is quantified, and describe its interrelation with other clinical features. In addition, it is essential to elucidate the current understanding of the neural networks underlying apathy and its three dimensions. These topics will be reviewed in the following sections before later delving into the presentation of apathy in one particular patient population, HD, that will be the focus of this Doctoral Thesis.

1.2 Apathy: A Complex Multidimensional Construct

1.2.1 Definition of Apathy

So, how is apathy defined? And what is its nosological status, or, in other words, how is it characterized? In 1991, Marin was the first to recognize apathy as a distinct neuropsychiatric syndrome (Marin, 1991). In this landmark paper, Marin defined apathy as a "loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness" (Marin, 1991). In this sense, apathy could occur independently from depression (i.e., emotional distress), which has since been empirically corroborated (M. L. Levy et al., 1998). At the same time, Marin recognized that apathy was described as a multidimensional construct by clinicians, including designations of poor initiative, reduced interest, and flat emotional affect, among others. Before we move forward to exploring the dimensions of apathy, it is important to further explore the concept of apathy as a syndrome vs. apathy as a symptom (**Box 1.1**).

Box 1.1. Apathy: A Symptom or a Syndrome?

According to Marin (1991), apathy as a syndrome is defined as a "loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness." In other words, syndromic apathy concerns *primary* apathy (Marin, 1991). Meanwhile, a loss of motivation due to disturbance of intellect, distress, or level of consciousness could be defined as apathy *secondary* to another condition, or apathy as a symptom. This may take the form of apathy as observed in major depressive disorder (Mulin et al., 2011; Yuen et al., 2014), secondary to emotional distress (Pagonabarraga et al., 2015), or, alternatively, secondary to dementia or delirium.

At this juncture, it is important to note that the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), does not characterize apathy as a syndrome or distinct disorder, but instead as a symptom that may manifest across a variety of diagnostic categories (American Psychiatric Association, 2013). This is also the case in the International Classification of Diseases, tenth revision (ICD-10) (World Health Organization, 1993). More recent approaches to the classification of mental health disorders, such as Research Domain Criteria (RDoC), champion a novel framework that integrates neuroscience with psychiatry (*Research Domain Criteria (RDoC) - National Institute of Mental Health (NIMH)*, 2024). In brief, RDoC

strives to classify mental disorders along the full range of a given dimension of observable behavior. This is opposed to the traditional binary categorization of the presence or absence of a psychiatric diagnosis (e.g., apathetic vs. non-apathetic). As an example, criteria associated with apathy spans process of approach motivation (including components of reward valuation, effort valuation/willingness to work, expectancy/reward prediction error, and action selection/preference-based decision-making), responses to reward attainment, reward learning, and habits (Thant & Yager, 2019). In this way, RDoC promotes a more targeted investigation of syndromes that may span diagnostic categories as well as its underlying pathophysiological mechanisms (Insel et al., 2010). In a related vein, this approach emphasizes the study of neural circuits that mediate specific behavioral functions, which may facilitate understanding of the neurocircuitry underlying transdiagnostic psychiatric features (Salamone et al., 2016).

At this point in time, the nosological position of apathy remains unclear. Nonetheless, the importance of capturing "pure apathy", or that which is independent of depression and reduced consciousness, is essential to further understand the neurological basis of apathy as a syndrome. This in turn may aid the selection of more homogenous patient subgroups for clinical trials and the identification of targets for precise treatment development.

Ultimately, based on clinical observations, Marin proposed a three-dimensional framework for the syndrome of apathy, which encompassed diminished goal-directed behavior, cognition, and emotional expression (Marin, 1991). This concept of apathy as a multidimensional construct was carried forward in subsequent definitions of apathy in the literature, reflected in **Table 1.1**. Note that terms that encompass each apathy dimension vary throughout the literature and that in some cases, a fourth dimension is also proposed.

Table 1.1. Dimensional definitions of apathy, primarily based on the three-dimensional model

Author (Date)	General definition	Dimensions
Marin (1991)*	Loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness	Goal-directed behavior, goal-directed cognition, emotional concomitants of goal-directed behavior
J. L. Cummings et al. (1994)	Less interested in or motivated for activities, plans, or conversations	Initiative, enthusiasm, emotions
Stuss et al. (2000)	An absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action	Arousal, executive, affective + social apathy
Starkstein (2000)*	Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture	Goal-directed behavior, goal-directed cognition, concomitants of goal-directed behavior (i.e., affective)
Robert et al. (2002)	A lack of interest, emotion, and motivation	Lack of initiative (behavioral), lack of interest (cognitive), emotional blunting (affective); includes subject's awareness of above symptoms
Sockeel et al. (2006)	A lack of motivation or lack of initiative; a set of behavioral, emotional, and cognitive features such as reduced interest and participation in the main activities of daily life, a lack of initiative, a trend towards early withdrawal from initiated activities, indifference, and flattening of affect	Intellectual curiosity, action initiation, emotion + self-awareness
R. Levy & Dubois (2006)	A quantitative reduction of voluntary, goal-directed behaviors	Auto-activation processing, cognitive processing, emotional-affective processing
Starkstein & Leentjens (2008)*	Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture	Goal-directed behavior, goal-directed cognition, concomitants of goal-directed behavior (i.e., affective)
Robert et al. (2009)*	Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture	Goal-directed behavior, goal-directed cognitive activity, emotion
Ang et al. (2017)	A disorder of motivation characterized by reduced action initiation and goal-directed behavior	Behavioral activation, emotional sensitivity, social motivation
Radakovic & Abrahams (2018)	Lack of motivation towards goal-directed behavior	Initiation, executive, emotional; includes self-awareness of above symptoms
Robert et al. (2018)*	A quantitative reduction of goal-directed activity either in behavioral, cognitive, emotional or social dimensions	Behavior/cognition, emotion, social interaction
Miller et al. (2021)*	Persistent or frequently recurring diminished initiative, interest, or emotions	Initiative, interest, emotional expression/responsiveness

* These studies include proposed diagnostic criteria for apathy.
Cognitive = enthusiasm, lack of interest, intellectual curiosity, goal-directed behavior and cognition, and executive
Emotional = affective, emotional blunting, goal-directed concomitants, and emotional-affective
Behavioral = initiative, action initiation, and auto-activation deficit

Fifteen years later, in 2006, another shift emerged in apathy's nosological position. This took place when R. Levy & Dubois defined apathy not as an internal state of motivation or initiative, which would require psychological interpretation of internal behavioral states, but rather as a quantitative reduction of goal-directed behavior, which they argued was directly observable (R. Levy & Dubois, 2006). In fact, Stuss and colleagues had also called for an objective behavioral measurement to facilitate assessment in clinical practice (Stuss et al., 2000). Even earlier, Marin himself had noted that, "In most instances, the presence of apathy is suggested by a deficit… in the overt behavioral evidence of goal-directed behavior" (Marin, 1991, p. 245). Nonetheless, with the work of R. Levy & Dubois, this concept was concretized as the operationalized definition of the syndrome of apathy.

For the purpose of this Doctoral Thesis, apathy is defined as an observable multidimensional syndrome of quantitative reduction in goal-directed behavior in the absence of depression or reduced consciousness. Neurocognitively, goal-directed behavior involves many steps to generate, initiate, execute, and control voluntary action. These include, among others, cost-benefit evaluation (e.g., reward/motivation), executive function (e.g., generating/deciding on a goal), and self-initiation of behavior (Le Heron et al., 2019; Steffens et al., 2022). As such, apathy may result from an abnormality in any of these processes, thereby giving rise to apathy dimensions: emotional, cognitive, and behavioral.

1.2.2 Apathy Dimensions

Similar to the categorization of apathy as a distinct syndrome, the conceptualization of apathy as a multidimensional construct also continues to evolve over time. As seen in **Table 1.1**, the proposed dimensions of apathy largely mirror the three-dimensional model originally propounded by Marin (1991). Indeed, the deconstruction of apathy mostly occurs according to behavioral, cognitive, and emotional components (R. Levy & Dubois, 2006; D. S. Miller et al., 2021; Radakovic & Abrahams, 2018; P. H. Robert et al., 2002, 2009; Sockeel et al., 2006; Starkstein, 2000; Starkstein & Leentjens, 2008). These three dimensions will be further illustrated below.

First, cognitive apathy is described as inertia of cognitive faculties needed to elaborate a goal-oriented behavioral plan. These cognitive processes encompass executive functions,

such as problem-solving (e.g., rule-generation, set-shifting, planning), cognitive flexibility, allocation of attention, fluency, and strategies to retrieve information from episodic or semantic memory (R. Levy & Dubois, 2006). According to some conceptualizations, cognitive apathy also encompasses decreased interest and curiosity. As a whole, individuals with cognitive apathy may report difficulty in planning an activity, task-switching, and focusing on an action. Statements from individuals suffering from cognitive apathy may include, "I find it difficult to organize future goals," and "I am no longer interested in learning new things." Regarding terminology, cognitive apathy generally covers enthusiasm, lack of interest, intellectual curiosity, goal-directed behavior and cognition, and executive apathy.

Second, emotional apathy is defined as blunted affect or diminished emotional responsiveness. This includes both spontaneous emotions and emotional reactions to the environment, whether to positive or negative events. In reward-based frameworks, emotional apathy has been described as the inability to connect emotional-affective signals with ongoing or forthcoming behavior (Husain & Roiser, 2018). In other words, emotional apathy involves deficits in leveraging socioemotional rewards to incentivize behavior (Wong et al., 2023). Recent criteria also includes empathy as a component of emotional apathy (P. H. Robert et al., 2018). Here, it is important to distinguish emotional apathy from depression; whereas the former presents with emotional flattening and lack of emotional responsiveness (i.e., *displaying* emotional emptiness), the latter manifests as dysphoria, heightened negative valence, pessimism or hopelessness (i.e., *feeling* emotional emptiness) (Brodaty & Connors, 2020; Stanton & Carson, 2016). Patients experiencing emotional apathy may endorse, "I feel indifference for many issues that I previously cared about," and, "I no longer feel emotions when I watch a film, read a book, or hear a joke." Emotional apathy encompasses terms such as affective apathy, emotional blunting, goal-directed concomitants, and emotional-affective apathy.

Third, behavioral apathy is represented by a loss of behavioral initiation and effort, with increased dependency on others to structure everyday activities. This Doctoral Thesis follows the conceptualization by R. Levy & Dubois (2006), in which the behavioral dimension of apathy is represented by auto-activation deficit (R. Levy & Dubois, 2006). Auto-activation deficit translates to a reduction in self-activating movement, speech or

thoughts, leading to the characteristic "empty mind" at its most severe form (R. Levy & Dubois, 2006). In this sense, this dimension can feasibly comprise both behavioral (movement) and cognitive (thought) domains (Dickson & Husain, 2022). According to R. Levy & Dubois (2006), there is a sharp demarcation between the reduction of self-generated actions and the preserved production of actions elicited by strong external solicitation (R. Levy & Dubois, 2006). Patients may describe this form of apathy with the following statements: "I need a push to get started on things" and "Other people need to ask me to do day-to-day chores." Literature has historically related severe forms of auto-activation-deficit to akinetic mutism, abulia, and Laplane syndrome (Bonelli & Cummings, 2007; Lhermitte et al., 1986; Prange et al., 2018). In parallel, some consider avolition (also referred to as abulia) and akinetic mutism to be on a spectrum of apathy. Akinetic mutism is considered the most extreme form (Németh et al., 1988), where the individual produces little to no self-generated speech or movement (Spiegel et al., 2018). Overall, behavioral apathy is largely synonymous with deficits in initiative or action initiation as well as auto-activation deficit in the literature.

Meanwhile, other apathy dimensions have been described, including social apathy (Ang et al., 2017; Stuss et al., 2000), which may reflect a transdiagnostic construct of social withdrawal (Porcelli et al., 2019). Self-awareness has also been considered a domain (Sockeel et al., 2006). However, it could be argued that self-awareness is frequently lost in those with apathy in general, resulting in the classic lack of concern and anosognosia (Mograbi & Morris, 2014; Rosen, 2011; Starkstein et al., 2010). For this reason, the Dimensional Apathy Framework of Radakovic & Abrahams (2018) portrays self-awareness (or lack thereof) as encapsulated by each of the three dimensions (Radakovic & Abrahams, 2018). On another note, in proposed diagnostic criteria for apathy in Parkinson's disease, emotional distress was considered a subdomain of apathy (Pagonabarraga et al., 2015). This reflects what is classically regarded in the literature as apathy as a symptom of depression. Lastly, five apathy subdimensions have recently been described for the translation of research from animal models to humans: self-care, social interaction, exploration, work/education, and recreation (Cathomas et al., 2015). This model emphasizes apathetic behaviors that can be objectively observed.

Overall, apathy is a complex behavioral construct that may result from dysfunction of different domains (i.e., cognitive, emotional, and auto-activation deficit). Already, specific apathy profiles have demonstrated greater prevalence in certain patient populations, such as cognitive apathy in Alzheimer's disease and emotional apathy in behavioral-variant frontotemporal dementia (Fernandez-Matarrubia et al., 2018; Kumfor et al., 2018; Wei et al., 2019). Delineating subdimensions of apathy in neurocognitive disorders has been highlighted as a research priority (Lanctôt et al., 2017). Given its complexity, the fractionation of apathy along its dimensions allows the study of its underlying components, which may in turn elucidate its pathophysiological underpinnings (Husain & Roiser, 2018).

As will be explored later, apathy profiles may be explained by different underlying neurobiological mechanisms, including structural brain correlates and neural networks. First, of course, it is important to consider how dimensions of apathy are assessed in clinical practice and in research, as well as the gaps in the literature. For the purpose of this Doctoral Thesis, the classic three-dimensional model is considered (R. Levy & Dubois, 2006). This framework is that which is most frequently assessed in the few apathy scales that quantify discrete apathy dimensions, as will be reviewed below.

1.2.3 Interim Summary I

Ultimately, the definition of apathy has changed over time, and there is currently a lack of a unified definition (**Table 1.1**). The most common classification of apathy follows the three-dimensional model of cognitive, behavioral, and emotional apathy. However, even today, the heterogeneity of descriptors and resulting methodologies used to assess apathy across studies pose a challenge in its investigation and treatment development. Unified operationalization of apathy and its subdimensions is imperative to promote research to improve clinical practice and, ultimately, the wellbeing of patients. In brief, operationalization refers to the translation of abstract conceptual ideas into measurable observations. The resulting definition of apathy should be generalizable enough to be practical, while also allowing the study of peculiarities of individual diseases or populations. Doing so would allow the pathological framework of apathy to be studied

along the lines of the transdiagnostic concept that it is. The next subsection will explore attempts to operationalize apathy through diagnostic criteria and apathy scales.

1.3 Operationalization of Apathy

1.3.1 Diagnostic Criteria of Apathy

In clinical practice, apathy continues to be diagnosed as a unitary construct. Nonetheless, since Marin's definition in 1991 (Marin, 1991), distinct dimensions have been recognized, together comprising the apathy syndrome. As described above, these encompass diminished goal-directed behavior, cognition, and emotional concomitants. Starting in the year 2000, Starkstein proposed one of the the first diagnostic criteria for apathy (Starkstein, 2000), which was later revised to specify the duration of symptoms (Starkstein & Leentjens, 2008), i.e., at least four weeks during most of the day. These efforts were the first attempt to structure the apathy diagnostic criteria in four parts: primary diagnosis, symptoms and duration, exclusionary criteria, and severity.

As apathy became increasingly regarded as an important and impairing psychiatric syndrome in neurocognitive diseases (Lanctôt et al., 2017), a task force was established in 2009 to adapt the above criteria for application in Alzheimer's disease and other neuropsychiatric disorders (P. H. Robert et al., 2009). The main change was to Criterion B, which addressed the dimensions of apathy. Principally, each dimension (behavioral, cognitive, and emotional) was now distinguished as self-initiated/spontaneous vs. environment-stimulated, or in other words responsiveness to internal vs. external stimuli.

This was followed by later a revision of the criteria, again by an international consensus group, for application in brain disorders (P. H. Robert et al., 2018). Here, the main modifications involved terminology and further changes to Criterion B. To start, apathy was finally defined in line with the definition proposed by (R. Levy & Dubois, 2006) as a directly observable behavior (i.e., a quantitative reduction of goal-directed activity), rather than a psychological interpretation of internal behavioral states (i.e., lack of motivation). In addition, the word 'domain' was replaced by the word 'dimension' to

account for their interrelated nature. Regarding Criterion B, main changes constituted the combination of the behavioral and cognitive components and the addition of a social component. This maintained the three-dimensional model of apathy, but in this case constituting behavior/cognition, emotion, and social interaction.

Most recently, The International Society for CNS Clinical Trials Methodology Apathy Work Group convened to devise diagnostic criteria for apathy specifically in neurocognitive disorders (D. S. Miller et al., 2021). Neurocognitive disorders can be considered a subgroup within brain disorders, and include the etiologies HD, Alzheimer's disease, Parkinson's disease, frontotemporal degeneration, cerebrovascular disease, traumatic brain injury, infections such as HIV, and substance use (Sachdev et al., 2014). According to the consensus survey (D. S. Miller et al., 2021), only 59.4% of the expert group agreed that loss of social activity should be considered an independent domain in this patient population. As such, the social domain was removed and behavioral and cognitive dimensions were again divided, now termed "initiative" and "interest," respectively. The emotional dimension was retained. Similarities and differences between proposed diagnostic criteria for apathy over time can be juxtaposed in **Table 1.2**.

Table 1.2. Proposed diagnostic criteria for apathy through the ages *(continued on next page)*

	Starkstein, 2000	**Robert et al., 2009**	**Robert et al., 2018**	**Miller et al., 2021**
A	**Lack of motivation** relative to the patient's previous level of functioning or the standards of his or her age and culture as indicated by either subjective account or observation by others.	**Loss of or diminished motivation** in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.	A **quantitative reduction of goal-directed activity** either in behavioral, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others.	The patient meets criteria for a syndrome of cognitive impairment or dementia (as defined by either ICD or *DSM-5* criteria).
B	Presence, along with lack of motivation, of at least one symptom belonging to **each of the following three** domains: *Diminished goal-directed behavior* 1. Lack of effort 2. Dependency on others to structure activity *Diminished goal-directed cognition* 3. Lack of interest in learning new things or in new experiences 4. Lack of concern about one's personal problems *Diminished concomitants of goal-directed behavior* 5. Unchanging affect 6. Lack of emotional responsivity to positive or negative events	Presence of at least one symptom in **at least two of the three** following domains for a period of at least four weeks and present most of the time: *Domain B1: Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:* - Loss of **self-initiated** behavior - Loss of **environment-stimulated** behavior *Domain B2: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:* - Loss of **spontaneous** ideas and curiosity for routine and new events - Loss of **environment-stimulated** ideas and curiosity for routine and new events *Domain B3: Loss of, or diminished, emotion as evidenced by at least one of the following:* - Loss of **spontaneous** emotion, observed or self-reported - Loss of emotional **responsiveness** to positive or negative stimuli or events	The presence of **at least 2 of the 3 following dimensions** for a period of at least four weeks and present most of the time *B1.* ***BEHAVIOUR & COGNITION****: Loss of, or diminished, goal-directed behavior or cognitive activity as evidenced by at least one of the following:* - General level of activity - Persistence of activity - Making choices - Interest in external issue - Personal wellbeing *B2. EMOTION: Loss of, or diminished, emotion as evidenced by at least one of the following:* - Spontaneous emotions - Emotional reactions to environment - Impact on others - Empathy - Verbal or physical expressions *B3.* ***SOCIAL INTERACTION****: Loss of, or diminished engagement in social interaction as evidenced by at least one of the following:* - Spontaneous social initiative - Environmentally stimulated social interaction - Relationship with family members - Verbal interaction - Homebound	The patient exhibits at least one symptom in **at least two of the following three dimensions** (B1 to B3). These symptoms have been persistent or frequently recurrent for a minimum of 4 weeks and represent a change from the patient's usual behavior. These changes may be reported by the patient themselves or by observation of others. *Dimension B1 Diminished* ***initiative****: Less spontaneous and/or active than usual self:* - Less likely to initiate usual activities such as hobbies, chores, self-care, conversation, work-related or social activities *Dimension B2 Diminished* ***interest****: Less enthusiastic about usual activities:* - Less interested in, or less curious about events in their environment - Less interested in activities and plans made by others - Less interested in friends and family - Reduced participation in activities even when stimulated - Less persistence in maintaining or completing tasks or activities *Dimension B3 Diminished emotional expression/responsiveness:* - Less spontaneous emotions - Less affectionate compared to usual self - Expresses less emotion in response to positive or negative events - Less concerned about the impact of their actions on other people -Less empathy

C	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	These symptoms (A-B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.	These symptoms (A-B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.	These symptoms cause clinically significant impairment in personal, social, occupational, and/or other important areas of functioning. This impairment must be a change from their usual behavior.
D	The symptoms are not due to diminished level of consciousness or the direct physiologic effects of a substance (e.g., a drug of abuse or a prescribed medication).	The symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).	The symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to **major changes in the patient's environment**.	These symptoms are not exclusively explained by psychiatric illnesses, intellectual disability, physical disabilities, motor disabilities, change in level of consciousness, or the direct physiological effects of a substance.
	Bold text indicates primary changes from previous definition. *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; ICD = International Classification of Diseases.			

Interestingly, some authors have proposed the paradox that, while apathy is difficult to define theoretically, it is easy to observe in clinical practice (P. H. Robert & Manera, 2021). However, in reality, apathy is often underreported by patients and underrecognized by outside observers. On the one hand, patients often lack insight into their illness, a concept known as anosognosia, which is especially prominent in neurological disorders and neurodegenerative disease (Rosen, 2011). Caregivers may attribute apathetic behavior to laziness or even an act of deliberate opposition (Landes et al., 2001; Mason & Barker, 2015; Stanton & Carson, 2016). Clinicians, meanwhile, may misdiagnose apathy as depression or anhedonia due to an overlap in symptoms (Landes et al., 2005; Treadway & Zald, 2011). All of these factors may contribute to the wide range of prevalence estimates reported for apathy across populations. As such, there is a call for concurrent apathy evaluation from multiple sources in research, including caregivers and clinicians, and corroboration of self-report measures.

As reviewed above, the current diagnostic criteria of apathy underscore distinct domains of goal-directed behavior. Nonetheless, in the literature, there is little known about the prevalence of these apathy profiles in various neurodegenerative populations and their neurobiological underpinnings. More recently, the properties of multidimensional apathy scales have been explored in specific groups of patients, which may begin to shed light on apathy sub-architecture and patient profiles. The subsequent section will delineate

various metrics that have been used to quantify apathy severity and frequency. While some instruments only measure apathy as a unidimensional construct, others are capable of capturing apathy along specific dimensions.

1.3.2 Quantifying Apathy

To date, there is no agreed-upon gold standard measurement to quantify apathy. As such, apathy is assessed using a variety of methods. These include measurement scales (e.g., dichotomous or Likert), observational ratings of behaviors, and structured or semi-structured clinical interviews. The chronological development of apathy instruments, together with modifications in the proposed diagnostic criteria for apathy, is illustrated in **Figure 1.1**. Of note, two recent reviews recommended the concurrent implementation of multiple apathy questionnaires in research to further investigate the phenomenology, etiology, and underlying neural correlates of apathy, as well as treatment (Mohammad et al., 2018; Passamonti et al., 2018).

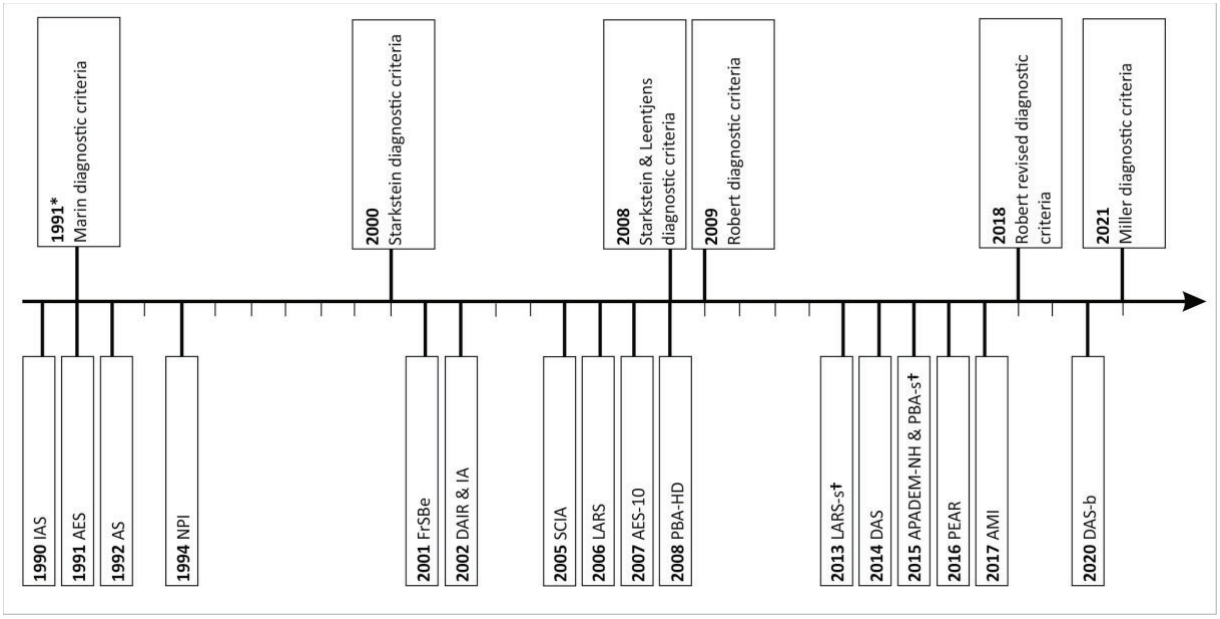


Figure 1.1. Chronological development of apathy instruments and diagnostic criteria from 1991 to present day. The asterisk (*) indicates the year that apathy was first described as a syndrome; the obelisk (†) highlights the apathy scales employed in this Doctoral Thesis. AES = Apathy Evaluation Scale; AES-10 = Apathy Evaluation Scale-10; AMI = Apathy Motivation Index; APDEM-NH = Apathy in Institutionalized Persons with Dementia, Nursing Home; AS = Apathy Scale; DAIR = Dementia Apathy Rating Scale; DAS = Dimensional Apathy Scale; DAS-b = Brief-Dimensional Apathy Scale; FrSBe = Frontal System Behavior Scale; IA = Apathy Inventory; IAS = Irritability Apathy Scale; LARS = Lille Apathy Rating Scale; LARS-s = Short-Lille Apathy Rating Scale; NPI = Neuropsychiatric Inventory; PBA-HD = Problem Behaviors Assessment for

Huntington's disease; PBA-s = Short-Problem Behaviors Assessment; PEAR = Pearson Environment Apathy Rating; SCIA = Structured Clinical Interview for Apathy.

While some instruments solely measure apathy as a global concept, there now exist multiple scales and criteria that quantify distinct apathy dimensions. Given the vast number of scales available, examination of the psychometric properties, such as reliability and validity, is necessary for comparison and selection of an optimal instrument (Radakovic et al., 2015). Select scales assessing global apathy and apathy dimensions are reviewed below, with a more general summary outlined in **Table 1.3**.

Table 1.3. Apathy scales and dimensions assessed *(continued on next page)*

Apathy scale (ref.)	Abbreviation	Source	Number of items	Dimensions assessed
Unidimensional				
Apathy Scale (Starkstein et al., 1992)	AS	Self-report, informant, and clinician	14-items	
Neuropsychiatric Inventory (Cummings et al., 1994)	NPI	NPI: Patient/informant NPI-Q: Questionnaire, self NPI-NH: Nursing home caregivers NPI-C: Clinician interview	12-items, 1-item for apathy (motivational aspects, as opposed to initiative and planning)	
Frontal System Behavior Scale (Grace & Malloy, 2001)	FrSBe	Self-report, informant-based, clinician interview	46-items, 14-items for apathy	
Dementia Apathy Rating Scale (M. E. Strauss & Sperry, 2002)	DAIR	Informant interview	16-items	
Problem Behaviors Assessment for Huntington's disease (Kingma et al., 2008)	PBA-HD	Clinician interview	40-items	
Short-Problem Behaviors Assessment (McNally et al., 2015)	PBA-s	Clinician interview	11-items, 1-item for apathy	
Multidimensional				
Irritability Apathy Scale (Burns et al., 1990)	IAS	Informant interview	5-items	
Apathy Evaluation Scale (Marin et al., 1991)	AES-S/I/C	AES-S: self-report AES-I: informant-based AES-C: clinician	18-items	
Apathy Evaluation Scale -10 (Lueken et al., 2007)	AES-10	Nursing home caregivers	10-items	
Apathy Inventory (P. H. Robert et al., 2002)	IA	Self-report and informant	3-items	

Structured Clinical Interview for Apathy (Starkstein et al., 2005)	SCIA	Clinician-interview with patient and caregiver	14-items	
Lille Apathy Rating Scale (Sockeel et al., 2006)	LARS	Self-report/patient interview, caregiver-based	33-items	
Short-Lille Apathy Rating Scale (Dujardin et al., 2013)	LARS-s	Self-report/patient interview, caregiver-based	12-items	
Dimensional Apathy Scale (Radakovic & Abrahams, 2014)	DAS	Self-report	24-items	
Apathy in Institutionalized Persons with Dementia, Nursing Home	APADEM-NH	Informant interview	26-items	
Pearson Environment Apathy Rating (Jao et al., 2016)	PEAR	Clinician observation	12-items	
Apathy Motivation Index (Ang et al., 2017)	AMI	Self-report	18-items	
Brief-Dimensional Apathy Scale (Radakovic, Gray, et al., 2020)	DAS-b	Self-report	9-items	
Apathy dimensions: Global = ; Cognitive = ; Behavioral = ; Emotional = ; Self-awareness = ; Social =				

In terms of global apathy measures, the Neuropsychiatric Inventory assesses twelve neuropsychiatric disturbances common in dementia, one of which is apathy (Cummings, 1997). The Neuropsychiatric Inventory is often referred to as the reference standard for assessing neuropsychiatric disorders and is the most frequently implemented measure for apathy in research and clinical settings (Radakovic et al., 2015), including clinical trials (Lanctôt et al., 2021). However, the use of a single domain for apathy does not allow the study of apathy dimensions. Likewise, the Frontal Systems Behavior Scale provides a measure for global apathy (in addition to executive dysfunction and disinhibition), but does not allow assessment of distinct apathy dimensions (Grace & Malloy, 2001).

Scales for the measurement of global apathy are also available in specific patient populations. This includes the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group, 1996) as well as the Problem Behaviors Assessment in HD (PBA) (Kingma et al., 2008), the latter of which is available in a short form, the short-

Problem Behaviors Assessment (PBA-s), for clinical use (Callaghan et al., 2015; McNally et al., 2015). In Parkinson's disease, the Unified Parkinson's Disease Rating Scale (Fahn et al., 1987; Pedersen et al., 2008) has been used, although the single-item for apathy has shown poor sensitivity, and therefore its use for apathy screening has been cautioned (Kirsch-Darrow et al., 2009).

Recent reviews recommend measuring multiple dimensions of apathy (Fritz et al., 2018; L. M. Jenkins et al., 2022; Misiura et al., 2019; Steffens et al., 2022). One of the first scales capable of capturing multiple dimensions of apathy was the Apathy Evaluation Scale (Marin et al., 1991), an 18-item questionnaire that quantifies apathy according to Marin's three dimensions: behavioral, cognitive, and emotional. Importantly, the Apathy Evaluation Scale is available in self-report, informant-based, and clinician-administered versions. This is especially useful for the interrogation and clinical evaluation of apathy in neurologic populations with anosognosia, when considering complementary sources may be beneficial. Similar to the Neuropsychiatric Inventory, the Apathy Evaluation Scale is often used as a reference standard in validation studies (Radakovic et al., 2015), and has already demonstrated sensitivity to change in clinical trials (Mohammad et al., 2018).

The Lille Apathy Rating Scale (LARS) is a structured interview that was devised to distinguish between apathy dimensions (Sockeel et al., 2006). The LARS was developed based on the main principles of apathy proposed by Marin (Marin, 1991). In total, the scale quantifies nine domains relevant to apathy: lack of interest, extinction of novelty seeking, reduced motivation, lack of concern, poor social life, reduction in everyday productivity, lack of initiative, blunted emotional response, and self-awareness (Sockeel et al., 2006). Factor analysis revealed four overarching dimensions: intellectual curiosity, action initiation, emotion, and self-awareness (Sockeel et al., 2006). These axes were largely in line with Marin's classifications, with the addition of the self-awareness component. While the LARS was initially devised for use in Parkinson's disease, it has been subsequently validated in schizophrenia (Yazbek et al., 2014) and dementia, including Alzheimer's disease, frontotemporal dementia, and primary progressive aphasia (Fernandez-Matarrubia et al., 2016). Widespread implementation of the LARS has since been recommended by the Movement Disorder Society Task Force (Leentjens et al.,

2008). Either the LARS or the Apathy Evaluation Scale are recommended in older adults and those with dementia (Burgon et al., 2021).

In addition, a short-form of the LARS (LARS-s) has been devised for practical and reliable use in everyday clinical practice (Dujardin et al., 2013). This version assesses seven of the nine original domains of apathy while also serving as an operative diagnostic tool. The LARS-s is the scale implemented in the present Doctoral Thesis, along with the PBA-s introduced above. Further details of these scales are provided in *§ 3.2.1 Neuropsychiatric Assessments*.

More recently, the Dimensional Apathy Scale was developed to quantify apathy subtypes independent of physical limitations and depression (Radakovic & Abrahams, 2014). In this way, it is suited for individuals with reduced mobility and movement disorders. The Dimensional Apathy Scale interrogates a three-dimensional structure of apathy that slightly deviates from Marin's model through assessment of executive, behavioral/cognitive initiation, and emotional dimensions (Radakovic & Abrahams, 2018). Similar to the LARS, the Dimensional Apathy Scale offers a brief version for use in clinical practice. This brief version uniquely includes a self-awareness question for each of the three domains evaluated (Radakovic, McGrory, et al., 2020).

1.3.3 Interim Summary II

Due to apathy's prevalence, caregiver burden, lack of treatment to date, and impact on prognosis and therapeutic engagement, it is critical to establish a standardized instrument for the quantification of apathy to facilitate advances in the field. At present, however, there is no agreed-upon gold standard apathy measurement. As a result, psychometric studies often utilize diagnostic criteria of apathy or a scale previously validated in a given disease as the *de facto* gold standard (Lanctôt et al., 2021; Mohammad et al., 2018; Mulin et al., 2011; Radakovic et al., 2015). In light of this, there is a need to explore the reliability and clinical validity of a standardized scale across neurological populations, especially one that has sufficient brevity to be implemented in clinical practice and trials. As of yet, clinical trials assessing apathy dimensions are virtually nonexistent (D. S. Miller et al., 2021).

When measuring apathy, it is important to capture "pure apathy" or "isolated apathy", i.e., that which is dissociable from depression and/or dementia. In the literature, this has been done by either excluding patients with depression and/or dementia (Ang et al., 2018; Den Brok et al., 2015; D'Iorio et al., 2017; Martinez-Horta et al., 2017; Pardini et al., 2016; Santangelo et al., 2018; Shin et al., 2017; Sousa et al., 2017; Sun et al., 2020) or controlling for depression and/or global cognitive impairment as a covariate (Martinez-Horta et al., 2016; Misiura et al., 2019; Reyes et al., 2009). The rationale for this will be elucidated in the following sections.

1.4 Apathy in the Context of Other Clinical Features

1.4.1 Apathy and Depression

Apathy has long been demonstrated to be dissociable from depression. This is true both clinically (M. L. Levy et al., 1998; Starkstein et al., 2005) and neurobiologically (Lanctôt et al., 2023; Onoda & Yamaguchi, 2015) across distinct neurocognitive disorders like Alzheimer's disease and frontotemporal dementia, as well as in healthy elderly without dementia. On clinical grounds, apathy has consistently been shown to be an independent construct in HD (Naarding et al., 2009), Parkinson's disease (Kirsch-Darrow et al., 2011), and major depressive disorder (Calabrese et al., 2014; Yuen et al., 2014).

At the same time, apathy and depression may share several overlapping signs and symptoms, which may distort clinical diagnosis (Starkstein et al., 2005). While there are certainly features of depression not seen in apathy (i.e., depressed mood, feelings of worthlessness/guilt, suicidal ideation), certain aspects of apathy may overlap with depression (i.e., psychomotor retardation, fatigue, altered sleep, weight loss, impaired concentration, anhedonia). Overall, six of the nine diagnostic criteria for major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5) may overlap with apathy. Therefore, care must be taken in the clinical evaluation to preclude misdiagnosis, while keeping in mind that syndromes may independently cooccur. Even within apathy scales, there is evidence that specific components of apathy and depression rating scales may overlap (Marin et al., 1993), yet apathy does not correlate with dysphoria per se (Landes et al., 2005).

Distinguishing apathy from depression is also critical for prognostic indications and selection of treatment. For example, antidepressants, specifically SSRIs (selective serotonin reuptake inhibitors), have been shown to worsen apathy in Parkinson's disease (Zahodne et al., 2012) and depressed elderly (Wongpakaran et al., 2007). In the research sphere, it is important to consider the aspects of apathy that are independent of depression, while simultaneously continuing to examine their overlapping features (e.g., anhedonia) (Husain & Roiser, 2018).

1.4.2 Apathy and Cognition

Apathy is associated with poor cognitive performance (i.e., memory, attention, visuospatial function, and executive function) in HD (Baudic et al., 2006; McAllister et al., 2021; Misiura et al., 2019; Sousa et al., 2017) as well as Parkinson's disease (Brown et al., 2019; D'Iorio et al., 2017; Santangelo et al., 2018), Alzheimer's disease (McPherson et al., 2002), and schizophrenia (Bortolon et al., 2018). Of these cognitive processes, the association between apathy and executive functions such as problem-solving (e.g., rule-generation, set-shifting, planning), attention, and retrieval has been especially well established in the literature. Again, this is true across neurologic populations. For example, apathy (as opposed to depression) was found to be associated with executive dysfunctions in HD (Baudic et al., 2006; Migliore et al., 2021; Sousa et al., 2017), Alzheimer's disease (McPherson et al., 2002), Parkinson's disease (Meyer et al., 2015; Szymkowicz et al., 2018; Zgaljardic et al., 2007), and cerebral small vessel disease (Le Heron, Manohar, et al., 2018; Lohner et al., 2017). In more detail, apathy (but not depression) was associated with deficits in implementing cognitive strategies involving executive tasks and recall in Parkinson's disease (Varanese et al., 2011). This relationship between apathy and executive dysfunction has also been demonstrated in healthy elderly, specifically in global apathy as measured by the LARS as well as the intellectual curiosity (cognitive) component (Montoya-Murillo et al., 2019).

Gathering this evidence, the link between apathy and executive dysfunction may be attributed to the fact that option generation, a skill impaired in cognitive apathy, requires an index of executive control (Husain & Roiser, 2018; G. Robinson et al., 2012). Indeed, apathy has long been considered a "frontal disease," arising from damage to or

dysfunction in nodes in frontostriatal circuits that also play a role in executive dysfunctions (D'Iorio et al., 2017; Leh et al., 2007; Martinez-Horta et al., 2017; Zgaljardic et al., 2006). For example, one study in healthy elderly demonstrated a link between apathy, executive deterioration, and reduced resting-state functional connectivity between a frontostriatal network (Kawagoe et al., 2017). The burgeoning evidence behind the neural network underlying apathy and more recently its subdimensions will be delineated in the subsequent section.

1.5 Neural Underpinnings of Apathy

1.5.1 Networks of Global Apathy

Across pathological conditions, apathy appears to be represented by a common underlying neural network. This, in part, sheds light on its pathophysiology as a transdiagnostic construct. Specifically, in neurodegenerative disease, psychiatric disorders, and brain injury, apathy is represented by disruption in frontostriatal as well as frontoparietal circuits (Kos et al., 2016; R. Levy & Dubois, 2006; Pagonabarraga et al., 2015; Stella et al., 2014; Theleritis et al., 2014). These cerebral pathways connect the frontal cortex (prefrontal, premotor, and supplementary motor areas) to the striatum (basal ganglia subregions comprised of the caudate, putamen, and nucleus accumbens) and to the parietal cortex, respectively. The frontostriatal and frontoparietal circuits are considered necessary for goal-directed behavior. However, the precise pathophysiological mechanisms of apathy are still only partially understood at this time, and various theoretical conceptions exist.

As an overview, three frontostriatal circuits have been implicated in apathy: (1) the dorsal circuit (dorsolateral prefrontal cortex (dlPFC) to dorsal basal ganglia), (2) the ventral circuit (orbital-ventromedial prefrontal cortex to ventral basal ganglia), and (3) the intermediary circuit (anterior cingulate-dorsomedial prefrontal cortex to the middle basal ganglia) (R. Levy, 2021), as illustrated in **Figure 1.2**.

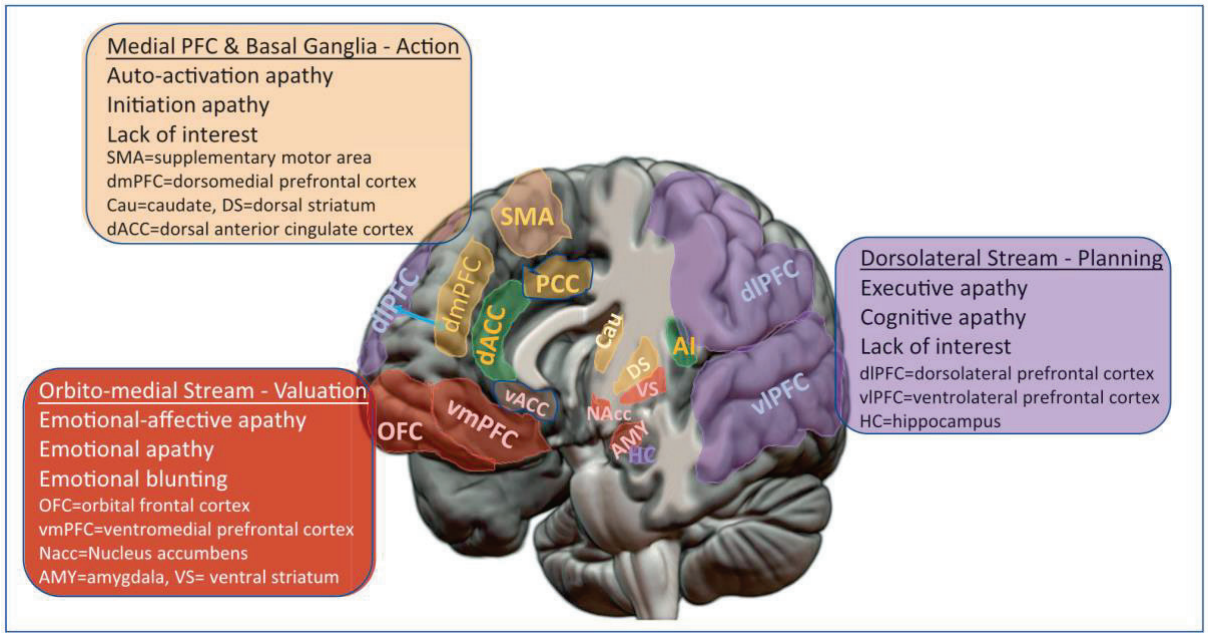


Figure 1.2. Three-dimensional model of apathy and proposed neurobiological correlates as concretized by (R. Levy & Dubois, 2006). Brain areas are color-coded to correspond with their hypothesized apathy dimension: cognitive apathy (purple), auto-activation deficit (orange), and emotional apathy (red). The dACC and AI (green) comprise the salience network, which monitors and switches between internal and external attention and facilitates motivation and decision-making. The dACC connects to the ventral, dorsal, and medial motor-networks, and can contribute to all three apathy subdimensions. AI = anterior insula; PCC = posterior cingulate cortex; vACC = ventral anterior cingulate cortex. *Figure adapted from* (Steffens et al., 2022) *under Creative Commons License.*

Concretely, apathy is strongly associated with structural brain atrophy or functional abnormalities within specific regions. These include the dorsal anterior cingulate cortex (dACC), medial prefrontal cortex, orbitofrontal cortex (OFC), and ventral striatum encompassing the nucleus accumbens (Husain & Roiser, 2018). These associations hold across clinical disorders and neuroimaging modalities (Le Heron, Apps., et al., 2018). Functionally, the striatum serves as a nexus that integrates domains such as reward prediction and motor execution (Gruber & McDonald, 2012; Schmidt et al., 2008). As a result, it is plausible that dysfunction in this region may produce apathy, which will be further exemplified below. Meanwhile, within neurodegenerative diseases specifically, degeneration and dysfunction in the orbitofrontal, dorsomedial, and dorsolateral prefrontal cortices and the temporal lobe have been related with apathy severity (Kos et al., 2016). When considering HD and Parkinson's disease, the mechanism of apathy may be explained by the hallmark progressive damage to frontostriatal circuits, a pathology that is well-established in these diseases (Aarsland et al., 1999; Craufurd et al., 2001).

Already, resting-state frontostriatal connectivity was reduced in a degree-dependent manner in apathetic individuals with Parkinson's disease (Baggio et al., 2015).

The frontoparietal network, often referred to as the cognitive control network or central executive network (L. M. Jenkins et al., 2022), has also been implicated in apathy across neurological populations (Kos et al., 2016; Tumati et al., 2019). In light of the relationship between apathy and executive dysfunction, it seems reasonable that apathy may also arise following deficits in this network. In Parkinson's disease, apathy has also been associated with a parietal-mediated disturbance of emotional processing (Dietz et al., 2013). More broadly, several studies highlight the involvement of the inferior parietal cortex in movement awareness and intentional movement (Desmurget & Sirigu, 2009; Hoffstaedter et al., 2013; I. H. Jenkins et al., 2000). Across neurodegenerative populations, apathy is most commonly related with damage in the prefrontal (60%), (inferior) parietal (40%), or temporal (20%) regions (Kos et al., 2016).

An alternative conceptual framework taking a neurocognitive perspective defines apathy as a deficit rooted in effort-based (i.e., cost-benefit) decision-making (Chong et al., 2016; Husain & Roiser, 2018; Pessiglione et al., 2018; Salamone et al., 2016). This framework considers the brain bases of normal motivated behavior along three systems (Le Heron et al., 2019). The valuation system (evaluating the putative reward and effort of a given future behavior) involves the ventral striatum and ventromedial prefrontal cortex; the motor system (producing the behavioral action) involves the middle cingulate cortex (MCC), supplementary area (SMA), and dorsal striatum; and the mediating system (integrating the two) involves the ventral striatum and anterior cingulate cortex (ACC). Historically, both the ventral striatum and ACC have been considered functional interfaces transferring information between the limbic and motor systems (Mogenson et al., 1980), thereby serving as a hub of cognitive and reward/effort processing (Vassena et al., 2014).

In general review, there is a striking similarity in the brain circuitry of apathy across patient populations, which has been consistently shown to involve frontostriatal and, more recently, frontoparietal networks. This includes the ACC, OFC, dlPFC, caudate, and ventral striatum. It could be hypothesized that distinct pathological mechanisms, such as localized neuronal death in stroke and trauma, frontostriatal degeneration in HD and Parkinson's disease, or alterations in white matter (WM) microstructure seen across

disorders all contribute to this network dysfunction, resulting in different routes to a similar clinical syndrome of apathy.

Yet, there is also regional variability across studies. As reviewed earlier, goal-directed behavior is comprised of a series of processes. This may explain the variance in brain regions implicated in apathy, in which specific brain areas and their interconnected circuits may give rise to different forms of apathy (i.e., apathy dimensions). Theoretically, disruption of any node in the proposed circuits may elicit apathy. Ultimately, there is a crucial need to study the differential neural processes underlying distinct aspects of goal-directed behavior, from intention and goal selection to action planning and execution. This will be delineated below according to the framework by R. Levy & Dubois (2006), which was later updated by R. Levy in 2012 and again in 2021 (R. Levy, 2012, 2021; R. Levy & Dubois, 2006).

1.5.2 Networks of Apathy Dimensions

Levy proposed that apathy is an observable clinical output that results from a range of mechanistic underpinnings, each of which represents a different component of goal-directed behavior (R. Levy, 2021). As reviewed above, these include cost-benefit evaluation (e.g., reward/motivation), executive function (e.g., generating/deciding on a goal), and self-initiation of behavior (Le Heron et al., 2019; Steffens et al., 2022). Because many steps are required to generate, initiate, execute, and control voluntary action, it is proposed that apathy may arise from abnormalities occurring at any point necessary to effectuate goal-directed behavior. As a result, there may be several different pathophysiological pathways that lead to the clinical syndrome of apathy, depending on which dimension is predominantly disrupted. In this Doctoral Thesis, the traditional triadic structure of apathy dimensions will be maintained, categorized as cognitive apathy, emotional apathy, and auto-activation deficit (R. Levy & Dubois, 2006). Empirical evidence supporting the underlying neural networks of this conceptualization will be described here. For a behavioral definition of each apathy dimension, please refer to *§ 1.2.2 Apathy Dimensions*.

1.5.2.1 Cognitive Apathy

First, cognitive apathy results from an impairment in executive functions needed to elaborate, organize, or manage a goal-oriented plan. Such functions, including task setting and monitoring, are effectuated by the dlPFC-basal ganglia circuit (referred to as the dorsal circuit) (Alvarez & Emory, 2006; Petrides & Pandya, 1999; Stuss, 2011; Stuss & Alexander, 2007). On neuropsychological testing, lesions to the dlPFC often produce poor performance in tasks such as the Stroop Color Word Interference Task (requiring sustained attention and response inhibition) and the Wisconsin Card Sorting Test (requiring mental flexibility and self-monitoring) (Bonelli & Cummings, 2007; Stuss et al., 2001). Clinically, disruption of the dorsal circuit results in susceptibility to distraction, organizational difficulties, and concrete or rigid thinking (Cummings, 1993). Although the specific dimension of cognitive apathy has been understudied, apathy is often observed in patients with lesions to the dorsal caudate nucleus (Bhatia & Marsden, 1994; Cognat et al., 2010; Mendez et al., 1989). In behavioral-variant frontotemporal dementia, a proposed model disease for the study of apathy and its neurocircuitry (Ducharme et al., 2018), increased atrophy of the right dlPFC has been associated with apathy (Massimo et al., 2009; Zamboni et al., 2008) as well as its planning component specifically (e.g., cognitive apathy) (Massimo et al., 2015).

1.5.2.2 Emotional Apathy

Second, emotional apathy is associated with deficits to the limbic system, specifically the orbital-ventromedial prefrontal-basal ganglia circuit (referred to as the ventral circuit). As implied by its name, this circuit originates in the OFC and the medial inferior frontal gyrus (Bonelli & Cummings, 2007). The limbic circuit is engaged by effort or reward-based decision-making tasks (Rogalsky et al., 2012; Schmidt et al., 2008). Moreover, lesions to the ventral striatum induce consequences for the emotional and motivational evaluation of a given environment in monkeys (Stern & Passingham, 1996). Clinically, emotional blunting is one of the principal features of orbital-medial prefrontal disturbance (Boone et al., 2003; Rosen et al., 2002). Profound apathy has also been reported in a rare case with bilateral, focal lesions to the basal ganglia that connect to the ventral circuit (Adam et al., 2013). Patients with schizophrenia experiencing negative symptoms such as amotivation showed reduced activation in the ventral striatum or OFC

in response to reward information (Avsar et al., 2013; Simon et al., 2010; G. P. Strauss et al., 2014).

In behavioral-variant frontotemporal dementia, where large-scale degeneration occurs in orbital and ventral prefrontal cortices, apathy is present in roughly 90% of individuals (Chow et al., 2009) and is part of the diagnostic criteria for this neurodegenerative disease (Rascovsky et al., 2011). Recently, a study using the LARS has specifically identified increased levels of the emotional apathy profile in those with behavioral-variant frontotemporal dementia, which was associated with hypometabolism in the medial frontal/anterior cingulate, orbitofrontal, and anterior insular cortices (Fernandez-Matarrubia et al., 2018). Beyond the ventral circuit, the ACC has been suggested as another area that could play a role in emotional apathy (Kos et al., 2016) given its function in reward processing and motivation, in addition to its associated frontostriatal circuit (Tekin & Cummings, 2002).

1.5.2.3 Auto-Activation Deficit

Third, as described earlier in *§ 1.2.2 Apathy Dimensions*, auto-activation deficit can develop into the most severe form of apathy. In turn, this apathy dimension is attributed to damage in a large swath of cognitive and limbic territories of the (medial) prefrontal cortex including the ACC, focal lesions in the basal ganglia, as well as WM tracts connecting these regions (R. Levy, 2021). In the basal ganglia, this includes the head of the caudate and anterior or dorsal nuclei of the thalamus (Bonelli & Cummings, 2007; Tekin & Cummings, 2002). In one study, bilateral lesions located in the caudate, putamen, or globus pallidus produced auto-activation deficit; patients were not able to modulate their performance according to the monetary incentive at stake, even despite the fact that the perception of value and motor force were not inferior to controls (Schmidt et al., 2008). To this effect, the authors concluded that auto-activation deficit reflected a disruption of incentive motivation, or the process that energizes behavioral action for an expected goal or reward, as has been previously described (Berridge, 2004; Pessiglione et al., 2007). Of note, the ventral striatum has been evidenced as a common motivational node capable of boosting both motor and cognitive systems (Schmidt et al., 2012), two functions classically impaired in auto-activation deficit.

In the prefrontal cortex, focal lesions can also result in severe apathy (Alexander & Stuss, 2000). More precisely, the ACC is considered a prominent hub of both cognitive and emotional/reward processing (Margulies et al., 2007; Rushworth et al., 2007). Specifically, the ACC connects the so-called ventral circuit (e.g., orbito-ventromedial and basal ganglia network) to the dlPFC and SMA, thereby serving to influence behavior by directing attention, modifying motivation, and initiating and monitoring an action (Bonelli & Cummings, 2007). Indeed, activity in the ACC, as well as its structural and functional connectivity with the SMA, has been correlated with apathy (Bonnelle et al., 2016). Lesions to the ACC are closely related to akinetic mutism, a state that leaves patients with intact consciousness, but outwardly indifferent to pain, thirst, or hunger (Bonelli & Cummings, 2007).

Although not included in the original model by R. Levy & Dubois, damage to the SMA or the presupplementary motor area (preSMA) may also lead to apathy, given their role in energization (Stuss & Alexander, 2007) and planning of intentional movements (Fried et al., 2011). The preSMA is a region associated with both motor preparation and cognitive tasks (Haggard, 2008; Morris et al., 2016; Nachev et al., 2008). Meanwhile, depending on whether the anterior segment of the medial prefrontal cortex or SMA are disrupted, arrest of spontaneous speech (Ardila & Lopez, 1984) and self-initiated movement (Deiber et al., 1991; I. H. Jenkins et al., 2000; Laplane & Degos, 1983; Thaler et al., 1988; von Giesen et al., 1994) can occur. In these cases, verbal repetition or externally generated actions are spared, consistent with the definition of auto-activation deficit, which is precisely a deficit of self-generated thoughts and actions.

In summary, damage to the anterior cingulate-dorsomedial circuit may affect the self-generation of goal-directed thoughts, speech, and behavior, thereby leading to apathy (Le Heron, Apps., et al., 2018). Additionally, Kos et al. (2016) proposed the inferior parietal cortex as potentially involved in this subtype (Kos et al., 2016), in line with its role in movement intention (Tumati et al., 2019). Research in healthy individuals suggests that self-initiated voluntary action is mediated through the recruitment of fronto-parieto-striatal areas (Haggard, 2008). Lastly, given the possible clinical severity of auto-activation deficit, widespread disruption of all three cognitive, limbic, and intermediary frontostriatal circuits are theorized to produce auto-activation deficit.

1.5.3 Interim Summary III

It is important to note that, while these three frontostriatal circuits have largely been described in isolation, this model is recommended as a general framework within the context of real-world neurobiology, where pathological processes can be much more complex. While previously conceived as separate parallel loops, it is now evident that these circuits interact and overlap with one another across both cortical and subcortical levels (Morris et al., 2016). Pathologically, neurologic insult and ensuing functional dysregulation often span multiple territories affecting distinct underlying circuits. As an example of this, in post-stroke patients, apathy has been related to a large subnetwork spanning the frontal lobe, insula, parietal lobe, temporal lobe, and basal ganglia (Yang et al., 2015).

Ultimately, while studies investigating the neural correlates of apathy dimensions are sparse, there is empirical evidence in line with R. Levy & Dubois's conceptualization (Stanton et al., 2013; Wei et al., 2019). These studies have evidenced a unique constellation of brain correlates that are distinct, albeit functionally interrelated. Overall, there is mounting evidence that apathy results from damage or dysfunction affecting the cognitive and/or limbic territories of the prefrontal cortex, the basal ganglia, and frontostriatal circuits, a system dedicated to the generation and updating of goal-directed behavior. Increased understanding surrounding the mechanistic underpinnings of apathy and its dimensions has the potential to promote personalized medicine in both prognosis and treatment avenues. For this Doctoral Thesis, we continue this line of investigation in the rare yet devastating HD, a disease defined by its hereditary nature and progressive degeneration of frontostriatal circuits and in which apathy is prevalent.

1.6 Huntington's Disease

1.6.1 An Overview of Huntington's Disease

HD is an inherited, autosomal dominant, neurodegenerative disorder caused by a cytosine-adenine-guanine polyglutamine (CAG) trinucleotide repeat expansion in the *HTT* gene on chromosome 4 (MacDonald et al., 1993). At ≥40 CAG repeats, the disease is

engendered with 90% penetrance (Tabrizi et al., 2022). Lower repeat lengths confer reduced penetrance (i.e., the repeats are necessary but not sufficient to cause the disease state). HD typically presents in mid-adulthood with the classic symptom triad of abnormal movements (especially chorea, but also bradykinesia and rigidity, among others), cognitive decline (e.g., executive functions, emotion recognition), and psychiatric disturbances (e.g., apathy, depression, and irritability) (Novak & Tabrizi, 2010). A progressive course over twenty to thirty years leads to increased dependency and ultimately death (Roos, 2010). Currently, there are no disease-modifying treatments.

As an inherited disorder, genetic testing can be utilized for either predictive or diagnostic purposes. Predictive testing can identify mutation carriers prior to diagnosis based on motor symptom onset (i.e., premanifest individuals), while diagnostic testing can provide unequivocal diagnosis in those presenting with clinical signs of the disease (i.e., manifest individuals) (Massey & McLauchlan, 2024). A greater number of CAG repeats elicits an earlier age of onset (Langbehn et al., 2010; Lee et al., 2012). As such, the CAG-age product (CAP) can be used as a marker of disease burden (Ross et al., 2014). In terms of prevalence, HD is rare, with an estimated 9.71 affected per 100,000 (Rawlins et al., 2016). At the same time, is the most common monogenic neurodegenerative disease. Given its genetic nature, HD has been deemed an ideal model for the study of neurodegeneration, especially in early stages before overt clinical symptoms emerge (Ross & Tabrizi, 2011). However, compared to other neurodegenerative disorders, HD is understudied.

Gray matter (GM) loss follows a dorso-ventral, caudo-rostral, and medio-lateral gradient (Kassubek et al., 2004; Vonsattel & DiFiglia, 1998). Specifically, degeneration begins in the dorsal striatum (i.e., caudate nucleus, putamen) of the basal ganglia (**Figure 1.3**), with basal ganglia structures outside the striatum generally involved in later stages (Aylward et al., 2004; Douaud et al., 2009; Georgiou-Karistianis, Scahill, et al., 2013). Striatal atrophy has been documented in premanifest HD gene-expansion carriers up to 15-20 years before predicted disease onset (Niccolini & Politis, 2014). Indeed, gray matter volume (GMV) has been found to be reduced cross-sectionally (Paulsen et al., 2010; Tabrizi et al., 2009) and longitudinally even in premanifest individuals (Kipps, 2005; Tabrizi et al., 2011, 2012). Atrophy extends to the cerebral cortex, showcasing a variable pattern even in later stages of the disease, which may partially explain phenotypic variability observed

in clinic (Tabrizi et al., 2009; Vonsattel et al., 1985; Waldvogel et al., 2014). The rate of atrophy is most pronounced in the basal ganglia; GMV in the caudate and putamen is regarded as the most sensitive biomarker of disease progression from an early stage (Aylward et al., 2011; Domínguez Duque et al., 2013; Tabrizi et al., 2013).

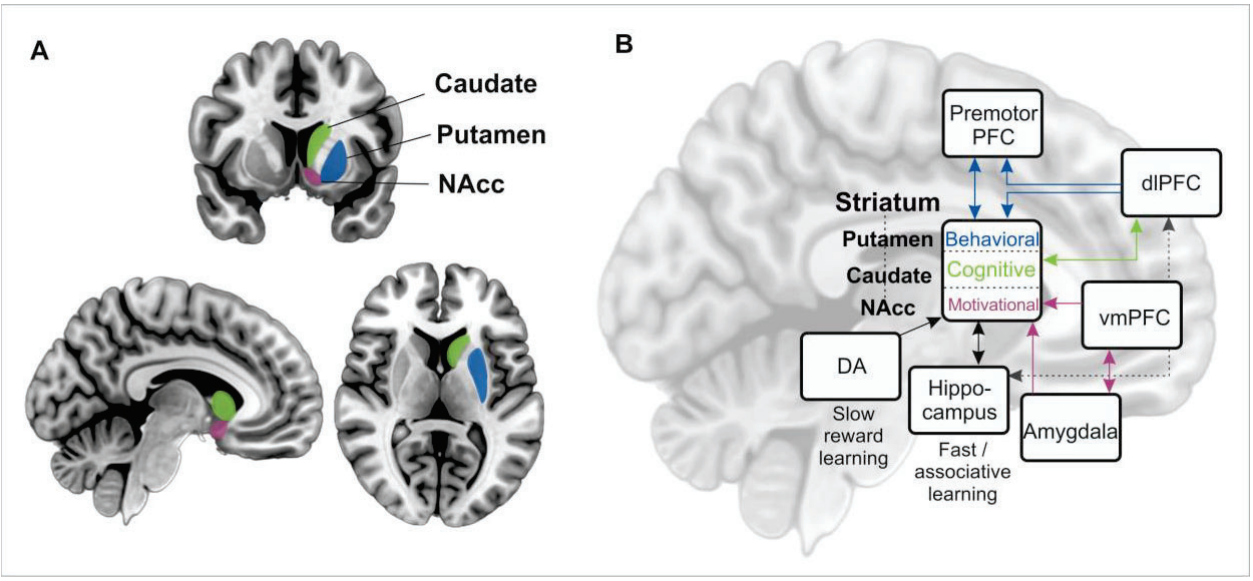


Figure 1.3. Structures of the striatum and associated frontostriatal circuits. (A) Components of the dorsal striatum (caudate nucleus and putamen) and ventral striatum (nucleus accumbens), the former being the first territories affected in Huntington's disease. Slice position in Montreal Neurological Institute coordinates from bottom left clockwise [x = -7, y = 9, z = 8]. **(B)** Interacting frontostriatal circuits as they contribute to action selection and initiation. Colored projections indicate the sensorimotor (i.e., behavioral), associative (i.e., cognitive), and limbic (i.e., motivational) circuits in blue, green, and purple, respectively. DA = dopamine; dlFPC = dorsolateral prefrontal cortex; NAcc = nucleus accumbens; PFC = prefrontal cortex; vmPFC = ventromedial prefrontal cortex. *Figure 1.3B adapted from* (M. J. Frank, 2011) *with permissions.*

Meanwhile, the importance of WM degeneration and resulting reduction in structural connectivity has been increasingly recognized in both premanifest and manifest stages (Zeun et al., 2019; J. Zhang et al., 2018). Indeed, one study evidenced selective vulnerability of cortico-striatal WM connections in premanifest stages, which became more widespread as the disease progressed (McColgan et al., 2015). Other work has demonstrated that atrophy of the striatum and WM occurs early in the disease course, prior to clinical symptoms (Hobbs et al., 2015; Tabrizi et al., 2012), with an acceleration of GM loss around the time of conversion to manifest HD (Scahill et al., 2013).

As a whole, degeneration in both GM and WM gradually and progressively gives rise to motor, cognitive, and psychiatric dysfunction (Paulsen et al., 2008). Ultimately, degeneration in HD classically follows a pattern of cortico-basal ganglia networks, which

substantially overlap with the frontostriatal tracts implicated in apathy (Camacho et al., 2018). **Figure 1.4** illustrates the progressive pattern of neurodegeneration in the WM and GM of subcortical and cortical territories.

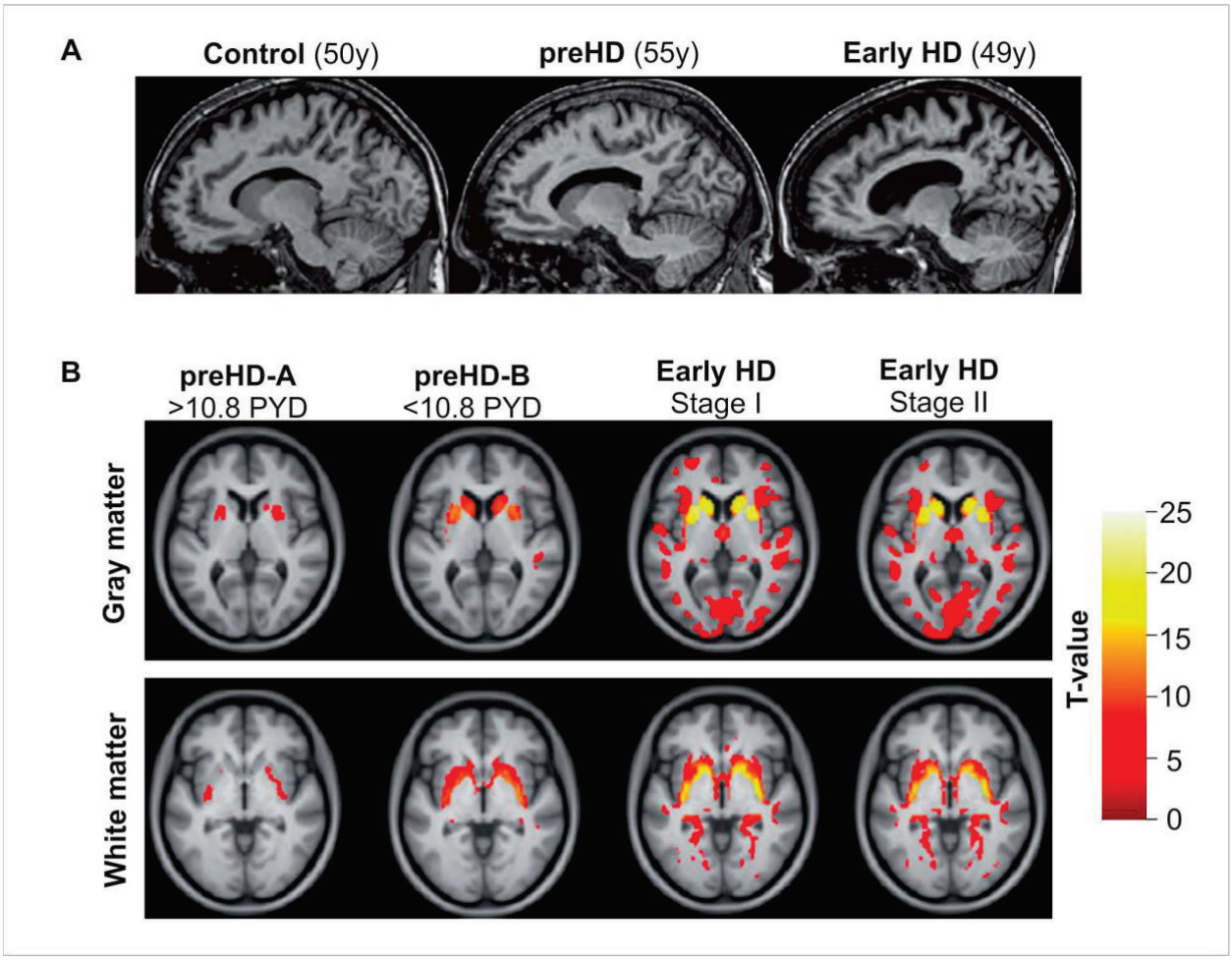


Figure 1.4. Whole brain and regional atrophy in HD groups compared to a healthy control. (A) 3T volumetric MRI scans illustrating progressive atrophy of subcortical and cortical areas in a 50-year-old control, 55-year-old with preHD, and 49-year-old with early manifest HD. **(B)** Voxel-based morphometry statistical parametric maps of gray and white matter differences among HD groups. Data adjusted for age, sex, study site, and intracranial volume. Results are corrected for multiple comparisons using family-wise error at the $P < 0.05$ level. HD = Huntington's disease; PreHD = premanifest HD; PYD = predicted years to diagnosis; y = years (age). *Figures adapted from* (Tabrizi et al., 2009) *with permissions.*

In light of its progressive motor symptoms, HD is classified as a movement disorder (Rosas et al., 2008). In current practice, clinical diagnosis is thus based on motor onset, demarcating the transition from the premanifest to the manifest stage. As a result, motor symptoms have conventionally been the primary focus of interventional studies (Sellers et al., 2020). However, patients and caregivers attest that psychiatric disturbances such as apathy bear the greatest burden on day-to-day functioning and quality of life, even beyond motor impairment (Eddy & Rickards, 2013; Paulsen et al., 2017; Ready et al.,

2008; Sellers et al., 2020; Youssov et al., 2022). Moreover, cognitive and psychiatric decline can present up to fifteen years prior to formal disease diagnosis, with executive dysfunctions, visuospatial disturbance, depression, and apathy being the most common (Aldaz et al., 2019; Martinez-Horta et al., 2016; Stout et al., 2011). In one large multicenter study, 42.4% of patients with HD reported at least one psychiatric or cognitive symptom in advance of motor symptoms, with an additional 22.3% reporting at least one of these symptoms concurrently with the onset of motor abnormalities (McAllister et al., 2021). This has led to recent calls for HD diagnostic criteria and classification taking into account non-motor symptoms (Considine et al., 2023; Reilmann et al., 2014; Ross et al., 2019; Vinther-Jensen et al., 2014). Ultimately, the significant impact of psychiatric signs across the spectrum of HD necessitates increased investigation in all gene-expansion positive individuals.

Overall, despite its monogenic etiology, there is much inter-individual heterogeneity in HD in disease onset (Roos, 2010), degenerative pattern (Rosas et al., 2008), and symptom prominence and progression (McAllister et al., 2021). Even between monozygotic twins with identical CAG repeat lengths, differences have been observed in both age of onset and in the type and timing of clinical signs (Anca et al., 2004; Friedman et al., 2005; Georgiou et al., 1999; Gómez-Esteban et al., 2007; Waldvogel et al., 2014). Still, the neurobiological origins of the wide range of phenotypic expression in HD remain unclear. Meanwhile, current neuroimaging research in HD is mainly limited to studying group differences, such as between patients and healthy controls. This approach overlooks inter-individual heterogeneity and possible disease profiles, as has been highlighted in recent research (Garcia-Gorro et al., 2019; Julayanont et al., 2020; Kim et al., 2015). In this way, we advocate for augmented study of individual differences inherent in HD, which has the potential to facilitate personalized management of these patients.

1.6.2 Apathy in Huntington's Disease

Over the course of HD, virtually all patients suffer from at least one psychiatric disturbance (Craufurd et al., 2001; Thompson et al., 2012). These include apathy, depression, irritability, anxiety, suicidal ideation, aggression, perseverative thinking and behaviors, obsessive-compulsive thinking and behaviors, hallucinations, and psychosis,

all of which are measured by the PBA, specifically designed for use in HD (Kingma et al., 2008). Of these psychiatric features, apathy has been found to be the most common, followed by depression and irritability (van Duijn et al., 2014). Specifically, prevalence of apathy in HD ranges from 52% to 76% (Paoli et al., 2017).

True to form, there is great fluctuation in the type and timing of psychiatric signs in HD. Beginning in premanifest individuals, a greater prevalence of apathy, irritability, and dysexecutive behavior is displayed when compared to healthy controls (Martinez-Horta et al., 2016). However, unlike motor and cognitive impairments, global psychiatric scores do not consistently align with disease progression (Duff et al., 2007; Epping et al., 2016; Ravina et al., 2008; Tabrizi et al., 2022).

In contrast, apathy is the one neuropsychiatric sign in HD that has consistently been shown to track disease progression (Tabrizi et al., 2013; Thompson et al., 2012), starting in the earliest stages (Matmati et al., 2021). In part, this may be attributable to the lack of effective treatments for apathy compared to depression, anxiety, and irritability. At the same time, it is plausible that this rise in apathy alongside disease progression may be due to the hallmark, unrelenting degeneration of frontostriatal circuits in HD, the same networks that are implicated in goal-directed behaviors (see *§ 1.5 Neural Underpinnings of Apathy*). In a recent review, apathy was defined as the only neuropsychiatric sign that may be considered a biomarker of disease progression, with the potential to inform disease diagnosis, prognosis, or monitoring (McColgan & Tabrizi, 2018). As such, apathy may serve as superb therapeutic target, even and especially in the preclinical phase of HD.

Apathy has also been associated with the presence of other common psychiatric features in HD, although with inconsistencies between studies. One large multicenter study revealed that apathy in mutation carriers was independently related with a positive psychiatric history for depression and obsessive-compulsive behaviors as well as a previous suicide attempt (van Duijn et al., 2014). However, the relationship between apathy and past depression in HD was non-specific, as a past episode of depression was associated with all neuropsychiatric features studied, with the exception of psychosis. More recently, apathy was non-specifically associated with depression across models in premanifest HD individuals and their controls (Misiura et al., 2019) as well as in manifest patients (Connors et al., 2023). A higher prevalence of apathy was also seen in mutation-

carriers with current suicidal ideation, although this was not distinguished from depression or other neuropsychiatric conditions (Hubers et al., 2012, 2013). Conversely, a prior study found that those with higher apathy were less likely to demonstrate suicidal ideation (Honrath et al., 2018). Considering another mood symptom, trait-based anxiety was found to predict apathy in HD (Poletti et al., 2022), although this was not evidenced in earlier studies (see (Dale & van Duijn, 2015) for review). In another vein, increasing apathy, but not depression, was significantly related with increasing irritability over time (Bouwens et al., 2015). Lastly, HD gene-expansion carriers with perseveration had a higher presence of apathy in addition to obsessive-compulsive behaviors and depression compared with matched carriers without perseveration (Liu et al., 2023). However, the majority of these studies do not assess the relationship between apathy and other neuropsychiatric symptoms over time. Therefore, there is a large gap in knowledge of longitudinal psychiatric trajectories in HD, especially at the individual level.

Conceptually, apathy has been grouped into 'frontal behaviors' together with disinhibition and executive dysfunction (Duff et al., 2010). This grouping has since been justified empirically in HD. For instance, factor analysis of the UHDRS behavioral assessment produced a drive/executive behavior factor comprised of apathy, perseveration, and compulsion, which was separate from the other factors of depression, irritability/aggression, and psychosis (Rickards et al., 2011). A distinct factor analysis of the PBA-s also produced an apathy component that was grouped with executive behaviors (preservation and obsessive-compulsive behaviors), separate from affective behaviors (depression/suicidality/anxiety) and irritability/aggression (Callaghan et al., 2015).

Furthermore, and similar to other neurologic populations, apathy in HD has been linked with cognitive impairment. This includes poorer performance on tests assessing memory, attention, and executive function (Baudic et al., 2006; Migliore et al., 2021), although one study found that apathy was specifically related with executive functions, and not with memory or language (Misiura et al., 2019). In a longitudinal study, HD individuals with persistent apathy over time exhibited significantly decreased performance in tests of executive function, such as the Symbol Digit Modality Test for psychomotor speed and Stroop word reading for processing speed and attention (Reedeker et al., 2011). Further supporting this relationship, apathy in premanifest HD gene-expansion carriers has been

shown to predict longitudinal decline in a cognitive composite score that included executive functions, such as attention, set-shifting, and planning and correction (Andrews et al., 2020).

Apathy is also related with loss of function independent of motor and cognitive symptoms (Hamilton, 2003) and depression (Connors et al., 2023; van Duijn et al., 2010). At baseline, apathy scores were a significant predictor of functional decline in early HD (Tabrizi et al., 2013) as well as unemployment (Jacobs et al., 2018) and financial impairment (Harris et al., 2022). Given that apathy significantly and negatively impacts quality of life and functional decline in HD, further research is warranted.

Despite its prevalence and impact, there is a paucity of research in the longitudinal trajectory of apathy, with most research based on cross-sectional studies. Furthermore, there is a relative dearth of longitudinal studies investigating individual differences in psychiatric evolution, even when considering apathy as a global construct (Connors et al., 2023; Ranganathan et al., 2021). Rather, most longitudinal studies that assess the natural course of psychiatric signs in HD, such as TRACK-HD, PHAROS, PREDICT-HD, and ENROLL (Biglan et al., 2013; Landwehrmeyer et al., 2016; Tabrizi et al., 2013; The Huntington Study Group PHAROS Investigators et al., 2016), largely focus on group differences defined *a priori* based on diagnostic status. As such, one gap in the field is the study of the diverse psychiatric signatures in HD, of which apathy is a key feature.

Finally, the above studies do not account for the multidimensional nature of apathy, instead investigating apathy as a unidimensional construct or one that is grouped with other behaviors (e.g., apathy with perseveration and obsessions/compulsions). Indeed, at the inception of the present body of work, no study had yet investigated apathy dimensions in HD. As such, in order to advance the understanding of apathy and its distinct neural correlates, it is important to consider apathy as a multidimensional construct. In addition, it is relevant to study apathy as separate from other neuropsychiatric features, including depression.

1.6.3 Structural Neural Correlates of Apathy in Huntington's Disease

Despite the fact that apathy is a major neuropsychiatric feature in HD, greatly impacts quality of life, and is a demonstrated marker of disease progression, only a limited number of MRI studies have explored the neural correlates of apathy in HD to date. This is in contrast to other more common neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and behavioral variant frontotemporal dementia, where studies of the underlying brain circuits of apathy are more prevalent (Kos et al., 2016; Steffens et al., 2022). Largely as a result of these investigations, we now have empirical evidence of the neurobiological basis of global apathy, as reviewed in *§ 1.5 Neural Underpinnings of Apathy*. However, to the best of our knowledge, no study outside the present Doctoral Thesis had empirically investigated the brain correlates of apathy dimensions in HD. Here, we explore the neuroimaging evidence for structural correlates (i.e., GMV, WM microstructural connectivity) of global apathy in HD. Please refer to **Table 1.4** for a summary of the methodological approaches and main findings for each study, noting that several studies report no structural findings for apathy. As an overview, **Figure 1.5** depicts regional GMV and WM tracts that have been related with apathy in HD. Because functional brain correlates (e.g., functional MRI, positron emission tomography, spectroscopy) are outside the scope of this Doctoral Thesis, select results are presented in **Table 1.4**, but are not discussed in depth.

Table 1.4. Summary of neural correlates of apathy in Huntington's disease *(continued on next page)*

Study	Sample size	Imaging modality	Analytical technique per brain correlate	Psychiatric scale	Covariates of no interest	Findings
Scahill et al. (2013)	**Track-HD** 239 combined preHD (120) and early HD (119) group	**Structural** T1-weighted MRI	**Structural** • GM volume (whole-brain VBM) • WM volume (whole-brain VBM)	PBA (severity × frequency)	Age, gender, study site, education, TIV, CAG repeat length, disease-burden	No relationship with apathy
Dumas et al. (2013)	**Track-HD Leiden** • 43 combined preHD (27) and early HD (16) group • 28 controls	**Structural** • T1- and T2-weighted MRI • Diffusion MRI	**Structural** • GM (# voxels per ROI GM volume) • WM (DTI, ADC and FA; ROI)	• BDI-II (depression) • FrSBe (apathy, executive dysfunction, disinhibition)	Age, gender	No relationship with apathy
Delmaire et al. (2013)	**Track-HD Paris** • 27 early HD • 24 controls	**Structural** • T1- and T2-weighted MRI • Diffusion MRI	**Structural** • GM volume (whole-brain VBM for group analyses, ROI for correlations) • WM (DTI, MD and FA; whole-brain VBM for group analyses, ROI for correlations)	PBA-s (severity × frequency)	Age, disease burden	↑ apathy a/w ↓ FA in bilateral WM of rectus gyrus
Gregory et al. (2015)	**Track-HD multisite** 84 combined preHD (39) and early HD (45) group	**Structural** Diffusion MRI	**Structural** WM (DTI, FA; whole-brain tract-based spatial statistics)	• Hospital Anxiety & Depression Scale (depression) • PBA-s apathy composite (severity × frequency) • PBA-s irritability composite (severity × frequency)	Age, sex, site and TIV ± medication	• No relationship with apathy • ↑ depression a/w ↓ FA in splenium of corpus callosum • ↑ irritability a/w widespread ↓ FA
McColgan et al. (2017)	**Structural** • 70 preHD • 81 controls **Functional** • 92 preHD • 94 controls	**Structural** • T1-weighted MRI • Diffusion MRI **Functional** rs-fMRI	**Structural** WM (DTI; streamline count from ROIs; binary and weighted) **Functional** rs-fMRI (magnitude of correlation from ROIs; binary and weighted)	• Hospital Anxiety & Depression Scale (depression) • Beck Depression Inventory II (depression) • Baltimore apathy scale, self-report	Age, gender, site, CAG repeat length ± medication	• No structural findings for apathy; ↑ apathy a/w ↓ functional connectivity in DMN • ↑ depression a/w ↑ functional connectivity in DMN, ↓ structural connectivity in cortico-BG
Baake et al. (2018)	171 combined preHD (91) and early HD (80) group	**Structural** T1-weighted MRI	**Structural** GM volume (ROI), cross-sectional and longitudinal	PBA-s apathy composite (severity × frequency and severity only); cutoff	Age, gender, group, site, CAG repeat length ± medication ± depression	Presence of apathy a/w ↓ thalamus volume (at baseline)

				≥2 clinically relevant		
Martinez-Horta et al. (2018)	40 early HD	**Structural** 3T T1-weighted MRI **Functional** PET/CT of 18F-fluorodeoxyglucose metabolism	**Structural** GM volume (whole-brain VBM) **Functional** 18F-FDG uptake (SUVr, whole-brain)	PBA-s apathy (severity × frequency); cutoff >2 clinically relevant	• Age, gender, education, CAG repeat length, other neuropsychiatric sx ± cognitive sx ± motor sx • TIV for GM analyses	• ↑ apathy a/w ↓ GM volume in bilateral amygdala, temporal cortex • ↑ apathy a/w ↓ glucose metabolism in SMA, ACC, fronto-polar PFC, superior medial PFC, and superior temporal gyrus
Misiura et al. (2019)	797 preHD	**Structural** T1-weighted MRI	**Structural** GM volume (ROI)	Apathy component of the UHDRS	Motor scores, CAP, depression ± years of education	↑ apathy a/w ↓ GM volume in caudate and putamen
Ceccarini et al. (2019)	• 15 preHD • 15 gene-negative controls • 12 community controls	**Structural** T1-weighted MRI **Functional** PET of CB_1R	**Structural** GM volume (whole-brain VBM *and* ROI) **Functional** CB_1R availability	• Beck Depression Inventory • State-Trait Anxiety Inventory II • PBA composite (apathy, irritability, depression)	• Age, CAG repeat length • TIV for GM analyses	• No structural findings for apathy, depression, or irritability • ↑ total behavioral scores and ↑ depression a/w ↓ CB_1R availability in PFC, OFC, ACC • ↑ factor 1 (apathy / depression factor) a/w ↑ CB_1R availability in PFC, vmPFC, ACC
Sampedro et al. (2019)	• 21 preHD • 19 early HD	**Structural** T1-weighted MRI **Functional** PET/CT of 18F-fluorodeoxyglucose metabolism	**Structural** GM cortical thickness (cortical at whole-brain; subcortical ROI) **Functional** 18F-FDG uptake (SUVr cortical at whole-brain; subcortical ROI)	PBA-s apathy (severity × frequency); cutoff >2 clinically relevant	• Age, sex, education ± CAG repeat length, UHDRS-TMS	• No structural findings for apathy • ↑ apathy a/w ↓ frontotemporal metabolism
Zeun et al. (2022)	**Track-ON HD** • 72 preHD • 85 controls **HD-YAS** • 54 preHD • 53 controls	**Structural** Diffusion MRI	WM connectivity (fixel-based; fiber density and cross-section in ROI tracts)	• Baltimore Apathy scale, self-report • Baltimore Irritability scale, self-report	• Age, gender, study site, education	↑ apathy a/w ↑ limbic corticostriatal fiber density and cross-section

PBA and PBA-s composite scores derived from (Kingma et al., 2008) and Callaghan et al. (2015), respectively. Disease burden calculated with formula in Penney et al. (1997). CAP scores calculated with formula in Y. Zhang et al. (2011). ACC = anterior cingulate cortex; ADC = apparent diffusion coefficient; a/w = associated with; BG = basal ganglia; CAP = CAG-age product; CT = computed tomography; CB_1R = cerebral type 1 cannabinoid receptor; DMN = default mode network; HD = Huntington's disease; HD-YAS = HD young adult study; FA = fractional anisotropy; GM = gray matter; MD = mean diffusivity; OFC = orbitofrontal cortex; PBA(-s) = (short-)Problem Behaviors Assessment; PET = positron emission tomography; PFC = prefrontal cortex; preHD = premanifest Huntington's disease; R = right; ROI = region-of-interest; rs-fMRI = resting state functional MRI; SMA = supplementary motor area; SUVr = standardized uptake value; sx = symptoms; TIV = total intracranial volume; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-TMS = Unified Huntington's Disease Rating Scale - Total Motor Score; VBM = voxel-based morphometry; vmPFC = ventromedial prefrontal cortex; WM = white matter; 18F-FDG = 18F-fluorodeoxyglucose metabolism; ± = with and without.

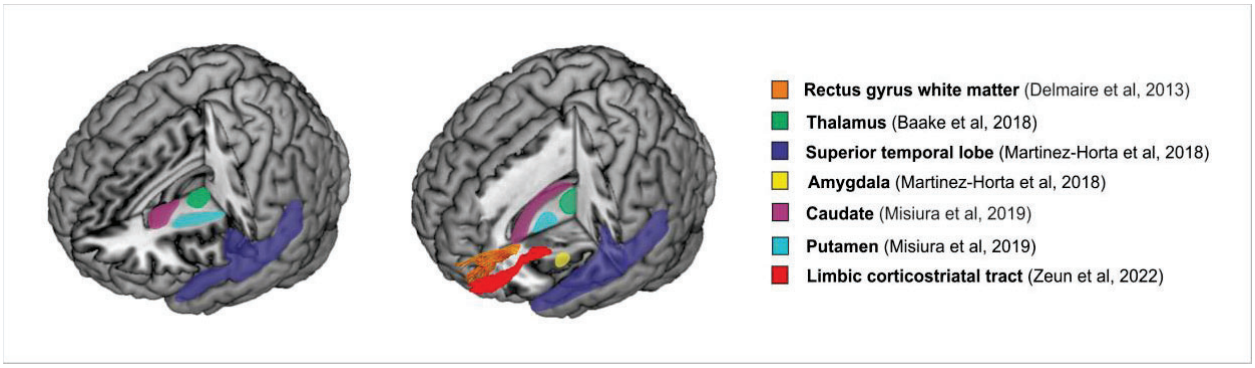


Figure 1.5. Structural neural correlates associated with apathy in Huntington's disease, together with their corresponding studies. Negative associations were found between apathy and gray matter volume across studies, in that higher apathy was related with lower gray matter volume. Regarding structural connectivity, apathy was associated with decreased white matter connectivity in the rectus gyrus in one study, in contrast to increased limbic corticostriatal fiber density and cross-section (i.e., less bundle atrophy) in another. Figures are illustrative and are not intended to represent exact anatomical results.

1.6.3.1 Gray Matter Volume

In parallel with the broader literature, apathy in HD is associated with dysfunction or atrophy along frontostriatal tracts. However, little is known about the specific GM nodes along these circuits that may be associated with apathy in HD. One study in mild manifest HD utilizing a whole-brain approach and controlling for various demographic and non-apathetic psychiatric features revealed a significant relationship between heightened apathy and decreased GMV in a large-scale network involving the bilateral amygdala and temporal cortex (Martinez-Horta et al., 2018). Non-significant associations included cortical (e.g., insula, SMA, ACC) and subcortical regions (e.g., caudate, putamen, and ventral striatum). The authors interpreted these findings as substantiation that apathy is subserved by a complex cortico-subcortical network that extends beyond the traditional frontostriatal conceptualization, encompassing reward and emotion-related nodes.

A two-year longitudinal study examined the relationship between seven subcortical regions-of-interest (ROIs) and change in apathy in a combined premanifest and manifest HD group (Baake, Coppen, et al., 2018). ROIs consisted of the caudate nucleus, putamen, nucleus accumbens, pallidum, amygdala, hippocampus, and thalamus. Longitudinally, there were no significant associations between change in apathy and change in volume in any subcortical structure, nor was there a linear association between initial volume and apathy score. However, logistic regression analysis did reveal a significant relationship

between the baseline volume of the thalamus and the presence or absence of apathy at the initial visit. The models were all run both with and without controlling for depression.

Another ROI approach analyzed the relationship between apathy and subcortical GMV in premanifest HD while also controlling for depression (Misiura et al., 2019). In this study, apathy was evaluated with the apathy component of the UHDRS (Huntington Study Group, 1996). Apathy demonstrated a significant negative relationship with both putamen and caudate volumes, but not thalamus volumes. The authors interpreted this to mean that the relationship between apathy and brain regions were specific to the basal ganglia in HD. These findings directly contrast those presented in Baake et al. (2018), in which only the thalamus volume significantly related with the clinical presence of apathy (although this relationship was specific to logistic regression and was not reproduced in linear regression) (Baake, Coppen, et al., 2018). Notwithstanding, the apathy scales and disease state selected differed between studies, cautioning comparability.

Next, in addition to WM connectivity, which will be discussed below, Dumas et al. (2013) assessed the possible link between behavioral signs like apathy and GMV in *a priori* ROIs: the corpus callosum, caudate nucleus, thalamus, prefrontal cortex, and sensorimotor cortex (Dumas et al., 2013). Behaviors were assessed with the Beck Depression Inventory II and the Frontal Systems Behavior Inventory (apathy, executive dysfunction, and disinhibition assessed separately) in a combined premanifest and early manifest group. No significant relationships between behavioral measures and GMV were found.

Ceccarini et al. (2019) investigated the relationship between behavioral symptoms (apathy, irritability, and depression) and structural and functional neuroimaging correlates in premanifest HD (Ceccarini et al., 2019). Behavioral symptoms were measured using the PBA composite scores (Kingma et al., 2008). Despite the fact that premanifest individuals did show smaller volumes in subcortical regions (e.g., caudate, putamen, and nucleus accumbens) compared to controls, no association was found between any behavioral measure and structural markers in either the whole-brain or volume-of-interest approach. However, functional findings were demonstrated with cerebral type 1 cannabinoid receptor binding using positron emission tomography. This is similar to another combined structural and functional study in combined premanifest and manifest HD individuals, where apathy was not related with structural measures

(cortical thickness), but was related with glucose hypometabolism in frontotemporal regions (Sampedro et al., 2019).

1.6.3.2 White Matter Connectivity

Studies of WM microstructural connectivity and apathy in HD are likewise limited and replete with discrepancies. To begin, Delmaire et al. (2013) interrogated the relationship between assorted clinical measures and WM connectivity in predetermined cortico-basal ganglia networks in early manifest HD (Delmaire et al., 2013). Apathy was found to be related with decreased fractional anisotropy (FA; a proxy for WM integrity) in the WM of the bilateral rectus gyrus. No other neuropsychiatric functions were assessed, and there was no note of controlling for depression in this study.

Next, when employing a whole-brain approach, this time in a combined premanifest and early manifest group, no significant relationship was discovered between apathy and FA (Gregory et al., 2015). This was in contrast to irritability and depression, which were related to widespread reductions in FA (irritability) and more localized reductions in the splenium and corpus callosum (depression) at different stages of disease progression. Another study also reported no relationship between apathy and WM connectivity (Dumas et al., 2013). For this study, premanifest and early manifest cohorts were again pooled together for correlation analyses with clinical metrics. However, in contrast to Gregory et al. (2015), this study did not find a relationship between WM connectivity and any behavioral measures, as assessed by the Beck Depression Inventory II and the Frontal Systems Behavior Inventory (apathy, executive dysfunction, and disinhibition assessed separately) (Gregory et al., 2015).

The lack of findings between apathy and structural WM connectivity defied the authors' own expectations. Potential explanations included the possibility of a non-representational sample (i.e., those with the most profound apathy or greatest changes in brain structure may be absent), or that apathy in HD is not related to WM microstructural changes. This second explanation, however, fails to acknowledge that apathy is widely accepted as a dysfunction of frontostriatal circuits, which may plausibly include WM microstructural connectivity (Chase, 2011; Le Heron, Apps., et al., 2018; R. Levy & Dubois,

2006), which has been empirically corroborated in neurodegenerative disease (Powers et al., 2014; Prange et al., 2019).

In addition, McColgan et al. (2017) examined the link between neuropsychiatric signs (e.g., depression and apathy) and both structural and functional connectivity in premanifest HD individuals (McColgan et al., 2017). The ROI approach focused on seventy cortical regions and six subcortical regions (caudate, putamen, and thalamus bilaterally). Depression was found to be significantly associated with both structural and functional connectivity maps, yet apathy only significantly correlated with functional (but not structural) connectivity. Of note, while this study utilized companion-reported measures for depression, the self-reported Baltimore apathy scale was chosen for apathy assessment due to incomplete data for the companion-reported scale. Although anosognosia may be present in HD, this is less of a concern in premanifest individuals with intact cognition, and good rater-agreement has been shown for this scale (Chatterjee et al., 2005).

Scahill and colleagues (2013) also demonstrated negative findings for correlations between psychiatric and structural markers (both GM and WM) (Scahill et al., 2013). When examining correlations with anatomical regions, premanifest and early manifest cohorts were combined. Similar to the above studies, PBA-s composite scores were used to assess apathy, affect, and irritability. Specifically, the authors state that there was little evidence of associations between the neuropsychiatric variables and volume reduction with the exception of a single voxel in the WM of the right lingual gyrus.

Lastly, one recent study in two independent premanifest cohorts analyzed WM connectivity via fiber density (i.e., intra-axonal volume) and cross-section, both of which are expected to decrease with neurodegeneration as a result of axonal bundle atrophy (Zeun et al., 2022). The authors performed probabilistic tractography specifically in seven corticostriatal and seven corticothalamic tracts using fixel-based metrics, which were previously shown to be more sensitive to WM atrophy in neurodegenerative disease (Mito et al., 2018). This work revealed an unexpected significant positive correlation between apathy and limbic corticostriatal fiber density and cross-section (Zeun et al., 2022). In this sample, apathy evaluation again entailed the Baltimore Apathy and Irritability scale, which may contribute to discrepancies in these results compares to previous studies. The

authors themselves state that these results should be interpreted with caution due to the fact that the apathy scores in premanifest HD were low and did not correlate with disease burden, in contrast to previous studies. All in all, they surmise that this may reflect the limited clinical utility of the Baltimore scale in premanifest individuals.

1.6.4 Interim Summary IV

Of note, many of the above studies utilized the PBA-s to quantify apathy, allowing for some level of comparison between studies (**Table 1.4**). However, there are still discrepancies in which component(s) of the PBA-s were used, from the isolated apathy domain (McNally et al., 2015) to the composite apathy domain consisting of apathy, perseveration, and disoriented behavior from previous factor analysis (Callaghan et al., 2015; Kingma et al., 2008). There are also differences in the scoring of apathy (from the product of severity × frequency to the score of severity or frequency alone), and the cut-off value at which clinically relevant apathy was determined. Lastly, because the PBA-s was devised for use specifically in HD, this scale has not yet been implemented in other neurodegenerative diseases. Lastly, it should be noted that assorted populations of HD participants were studied, meaning the generalizability of the results with other stages of the disease should be interpreted with caution.

In conclusion, the structural neurobiological mechanisms of apathy are understudied and bear many inconsistencies. These discrepancies may stem from methodological differences in measurement scales, selected sample population, approach of imaging analysis (e.g., whole-brain vs. ROI), and inclusion of covariates of no interest, as highlighted above (**Table 1.4**). This, coupled with the fact that apathy has been linked to consistent neurobiological substrates in other neurodegenerative disease (see *§ 1.5 Neural Underpinnings of Apathy*), calls for further investigation of this topic in HD.

Chapter 2
Research Aims

Chapter 2 | Research Aims

Apathy is a complex multidimensional and transdiagnostic psychiatric disturbance of yet unknown etiology that is prevalent across many neurocognitive disorders, including HD. As reviewed in *§ Chapter 1 | Introduction*, apathy is still being defined at the nosological level (D. S. Miller et al., 2021), with much to understand in terms of individual differences in prognosis and neurobiological correlates. As such, the overarching aim of this Doctoral Thesis was to describe apathy as a multidimensional construct in HD, while investigating its structural neurobiological underpinnings and longitudinal relationship with associated psychiatric features of the disease.

To this end, the specific Research Aims are outlined below, together with the four studies that delved into these questions (**Table 2.1**). The framework for each study is then explicated in more detail in the following pages.

Research Aim 1: Characterize apathy as a multidimensional construct using the LARS-s in HD, while assessing the reliability, validity, and dimensionality of the LARS-s

- **Study 1:** Utilized the LARS-s to assess multidimensional apathy profiles conceptually, based on previous research
- **Study 3:** Employed factor analysis to probe apathy dimensions of the LARS-s in HD through a data-driven approach; Analyzed the psychometric properties of the LARS-s, including reliability and clinical validity

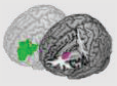
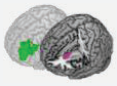
Research Aim 2: Shed light on the structural neurobiological correlates of apathy and its dimensions in HD through multimodal neuroimaging, including WM connectivity and GMV

- **Study 1:** Delineated specific cortico-striatal WM tracts and explored microstructural connectivity using diffusion tensor imaging (DTI) with tractography in relation to apathy and its dimensions
- **Study 2:** Elucidated longitudinal GMV correlates of global apathy using voxel-based morphometry (VBM) at the whole-brain level
- **Study 3:** Assessed cross-sectional GMV correlates of apathy and its dimensions using VBM at the whole-brain level

Research Aim 3: Explore longitudinal apathy progression in HD with respect to initial brain vulnerabilities as well as its interrelation with other prominent psychiatric features in HD

- **Study 2:** Examined whether initial brain vulnerabilities in GMV may predict the longitudinal severity and time course of apathy in HD
- **Study 4:** Implemented a novel unsupervised clustering algorithm to stratify HD individuals based on their psychiatric disease trajectory, thereby investigating the longitudinal interrelation between apathy and other prominent psychiatric features in HD, including depression, irritability, and perseverative/obsessive-compulsive behaviors

Table 2.1. Overview of how three Research Aims were addressed by each Study

Research Aim	Study 1	Study 2	Study 3	Study 4
1	Dimensional apathy 		Dimensional apathy  Psychometrics 	
2	WM 	GMV 	GMV 	
3		Longitudinal  Brain vulnerability 		Longitudinal  Interrelation with psych features 

GMV = gray matter volume; WM = white matter.
Research Aim 1: Characterize apathy as a multidimensional construct using the LARS-s in HD, while assessing the reliability, validity, and dimensionality of the LARS-s
Research Aim 2: Shed light on the structural neurobiological correlates of apathy and its dimensions in HD through multimodal neuroimaging, including WM connectivity and GMV
Research Aim 3: Explore longitudinal apathy progression in HD with respect to initial brain vulnerabilities as well as its interrelation with other prominent psychiatric features in HD

Study 1: White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease

In this first study, we investigated individual differences in apathy as a multidimensional construct in HD and its underlying relationship with WM microstructure of cortico-striatal connections. To this aim, we first categorized the apathy domains measured by the LARS-s into three dimensions (i.e., cognitive, emotional, and auto-activation) based on previous research. Next, we assessed global apathy and each of the three subdomains in HD individuals across premanifest and manifest stages, as well as in healthy control participants. Given that apathy is prevalent in HD and tracks HD progression, we hypothesized that apathy levels would be greater in both premanifest and manifest HD individuals compared to controls, and more so in advanced disease stages. In addition, we expected that apathy levels would be associated with clinical disease progression measures and that cognitive apathy specifically would relate with cognitive dysfunction.

Next, we investigated whether individual differences in specific cortico-striatal tracts predicted global apathy and its subdomains. To do so, we carried out *in vivo* virtual dissections of three cortico-striatal WM tracts in DTI space, thereby characterizing the dorsolateral prefrontal cortex to caudate nucleus tract (dlPFC-cn), the frontostriatal tract connecting the caudate and preSMA/SMA (FST), and the uncinate fasciculus (UF). We subsequently extracted proxy measures of WM structural integrity (e.g., mean diffusivity (MD)). We hypothesized that each apathy dimension would be represented by reduced connectivity in distinct WM tracts. In particular, we predicted that cognitive apathy would be significantly associated with decreased integrity in dorsal, cognitive tracts (i.e., dlPFC-cn, FST), emotional apathy with the ventral tract (i.e., UF), and auto-activation deficit with widespread dysfunction in both dorsal and ventral tracts (i.e., FST and UF).

Study 2: Gray matter vulnerabilities predict longitudinal development of apathy in Huntington's disease

When considering the underlying brain correlates of apathy in HD, recent studies (including **Study 1** of this Doctoral Thesis) have revealed that apathy is subserved by a complex organization of subcortical and cortical regions that span cognitive and limbic territories. However, the majority of these studies are cross-sectional. As such, their

applicability in delineating longitudinal changes in both clinical measures and brain atrophy in a progressive neurodegenerative disorder is limited.

To address this gap in the field, **Study 2** sought to identify whole-brain GMV vulnerabilities that may predict longitudinal apathy development, compared with depression and executive dysfunction, in HD over a period of up to six years. To this aim, we first employed longitudinal VBM at the whole-brain level to identify regions where GMV atrophy may describe changes in apathy severity across two time points. We hypothesized that a greater loss of GMV would be associated with a larger increase in apathy severity over time. We next employed a generalized linear mixed-effects model to elucidate whether the initial and specific GMV vulnerability identified by VBM could successfully predict the longitudinal development of apathy at the individual level. We predicted that regional vulnerability (i.e., lower initial volumes) would be associated with more severe and rapid progression in apathy presentation over time.

Study 3: Delineating apathy profiles in Huntington's disease with the short-Lille Apathy Rating Scale

In **Study 1**, we utilized the LARS-s to study apathy along its three dimensions utilizing a top-down approach, while also disentangling the WM microstructure changes that may underlie individual differences in apathy in HD. Following this, in **Study 3**, we wished to further this line of research through two aims: (1) assess the psychometric properties and dimensionality of the LARS-s as a practical tool for the measurement of apathy dimensions in HD in clinical practice by employing a data-driven approach, and (2) explore the potential relationship between GMV and apathy profiles. First, we analyzed the reliability and clinical validity of the LARS-s in HD. We strove to demonstrate that the LARS-s would possess both reliability and internal consistency, as well as convergent validity with apathy (i.e., PBA-s apathy score) and discriminant validity against depression (i.e., PBA-s depression score) when administered in HD. Next, in congruence with the three-dimensional framework of apathy dimensions (R. Levy & Dubois, 2006), we hypothesized that factor analysis would produce three principal components.

With regards to the second aim (e.g., VBM analysis), we expected that individuals with higher levels of global apathy as measured by the LARS-s would demonstrate decreased

GMV in cortical nodes pertaining to frontal-basal ganglia circuits previously demonstrated to be involved in apathy in HD (as measured by the PBA-s) and other neurological populations (Kos et al., 2016; Martinez-Horta et al., 2018; Pagonabarraga et al., 2015). Lastly, stemming from the results of **Study 1**, we hypothesized that such GM nodes may also reflect variability in apathy profiles along different domains. While this was an exploratory analysis, we proposed that distinct neurobiological underpinnings would underlie each apathy subdomain, spanning nodes across cognitive, motor, and limbic networks. Specifically, we anticipated that cognitive apathy would be associated with dorsal (associative) regions, emotional apathy with ventral (limbic) regions, and auto-activation deficit with widespread dorsal and ventral regions, as well as the basal ganglia.

Study 4: Mapping longitudinal psychiatric signatures in Huntington's disease

In the above studies, we investigated how individual differences in apathy and apathy dimensions, may be explained by heterogeneity in underlying brain substrates, both cross-sectionally and longitudinally. At this juncture, we wished to further characterize how apathy was interrelated with the progression of other prominent psychiatric disturbances in HD over time. More precisely, we sought to stratify HD gene-expansion carriers into subgroups that share patterns of longitudinal psychiatric trajectories utilizing a novel unsupervised clustering approach first demonstrated in (Giannoula et al., 2024). This framework thereby allowed the quantification of individual differences in psychiatric features across four psychiatric domains (i.e., depression, irritability, apathy, perseverative/obsessive-compulsive behaviors) at each point in time across a range of degrees of severity. In light of known heterogeneity in HD psychiatric manifestations, we hypothesized that the clustering algorithm would result in a range of clusters characterized by varying psychiatric signatures across the four domains. Additionally, given that psychiatric disturbances are known to present up to fifteen years prior to HD diagnosis by motor onset, we anticipated that clusters would not be limited to delineation along premanifest and manifest diagnostic status. With regard to apathy specifically, we expected that many clusters would demonstrate increasing apathy over time.

Chapter 3
Methods

Chapter 3 | Methods

A global overview of the methodology of this Doctoral Thesis is delineated in the present chapter. This includes information on participants, clinical evaluation including neuropsychiatric assessments, MRI acquisition and processing, and statistical analyses. More detailed methods are described in each individual study in *§ Chapters 4 – 7 | Results*.

3.1 Participants

Participants consisted of 47 HD gene-expansion carriers and 35 healthy control participants who matched for age ($t(79) = 0.05$, $P = 0.959$), sex ($t(69.8) = 1.65$, $P = 0.103$), and years of education ($t(78) = -1.31$, $P = 0.194$). Control participant data was utilized in two phases of the analysis: 1) to compare apathy levels and 2) to explore WM microstructure disturbance.

HD individuals were grouped into premanifest ($N = 22$) and manifest ($N = 25$) stages based on their UHDRS diagnostic confidence score for motor abnormalities at the initial visit (Huntington Study Group, 1996). Four participants who were initially classified as premanifest transitioned to a manifest state over time and are identified as phenoconverters. On average, participants completed 4.12 ± 1.54 assessments with a mean inter-assessment duration of 13.96 ± 4.04 months. Thirty-seven participants (80.4%) completed at least three visits, while nine participants completed one or two visits. This resulted in 189 total psychiatric evaluations.

Thirty-three HD gene-expansion carriers also received an MRI scan on their second visit at 18 ± 6 months follow-up. Due to scheduling conflicts, eleven HD participants did not return to complete their second scan. Three HD and one control participant were claustrophobic and so did not participate in either scan.

Because this Doctoral Thesis focused on psychiatric features, which may present prior to motor onset and formal diagnosis (Martinez-Horta et al., 2016; Thompson et al., 2012), the disease was studied as a continuum. This means that all participants were confirmed HD gene-expansion carriers at baseline (43.89 ± 3.00 CAG repeats). No participants reported previous history of a neurological disorder other than HD. All individuals

provided written informed consent, and ethical approval was granted by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975. All research was performed in accordance with relevant guidelines and regulations.

3.2 Clinical Evaluation

3.2.1 Neuropsychiatric Assessments

3.2.1.1 Lille Apathy Rating Scale, Short-Form

The LARS-s was employed to study apathy dimensions (Dujardin et al., 2013). This structured interview contains twelve discriminant items from seven domains for apathy detection: daily productivity, interests, taking the initiative, novelty seeking, motivation and voluntary actions, emotional responses, and social life. Example questions include, “What are you interested in?” and “Do you take part spontaneously in daily living activities, or do you need to be asked?” In the present study, global apathy is measured as the total score (range: 15 to +15) of the LARS-s. Higher scores indicate more severe symptoms. The cut-off for clinically relevant global apathetic syndromes is defined as a score > −7 (Dujardin et al., 2013).

3.2.1.2 Problem Behaviors Assessment, Short-Form

The PBA-s was designed for the evaluation of neuropsychiatric symptoms in HD and is administered as a semi-structured interview in the presence of the main caregiver or other knowledgeable informant (Craufurd et al., 2001; Kingma et al., 2008). The scale consists of 11 items: depressed mood, suicidal ideation, anxiety, irritability, angry or aggressive behavior, lack of initiative (apathy), preservative thinking or behavior, obsessive–compulsive behavior, paranoid/delusional thinking or behavior, hallucinations, and disoriented behavior. Scores are calculated as the product of frequency × severity (range: 0 to 16 for each symptom). Higher scores indicate more severe/frequent symptoms.

In certain analyses, non-apathetic neuropsychiatric disturbances were calculated as the sum of all 10 additional (non-apathetic) items of the PBA-s, allowing the examination of

apathy as an independent neuropsychiatric symptom from the others. Similarly, non-depressive neuropsychiatric disturbances (all but depressed mood, suicidal ideation, and anxiety (Craufurd et al., 2001; Tabrizi et al., 2009)) and the total PBA-s score were taken into account in models of depression and executive dysfunction, respectively.

3.2.2 Additional Huntington's Disease Clinical Assessments

Additionally, all participants were assessed with the UHDRS motor (UHDRS-TMS) and cognitive (UHDRS-cogscore) evaluation (Huntington Study Group, 1996). The UHDRS-TMS assesses the motor features of dysarthria, chorea, dystonia, gait, postural stability, and oculomotor function. The UHDRS-cogscore includes the F-A-S test (phonetic verbal fluency) and the Symbol Digit Modalities Test (psychomotor speed) as well as the word-reading, color-naming, and interference components of the Stroop Test (processing speed, attention, and inhibitory control). A lower UHDRS-cogscore, in contrast to higher UHDRS-TMS and PBA-s scores, represents worse functioning. In addition, total functional capacity (TFC) was employed as a measure of independence in daily activities, ranging from thirteen (full capacity) to zero (total incapacity) (Huntington Study Group, 1996). TFC has been shown to be reliable based on radiographic measures of HD progression (Young et al., 1986). Participants underwent a maximum total of six longitudinal visits for clinical evaluation, including the baseline assessment.

All evaluations were carried out by neuropsychologists and psychiatrists specializing in movement disorders. To further describe the HD sample, we computed the standardized CAP score (CAP = 100 × age × (CAG – 35.5) / 627), a proxy measure of HD state (Ross et al., 2014). Medication use (i.e., SSRIs, SARIs, NASSAs, NSRIs, NDRIs, benzodiazepines, tetrabenazines, antipsychotics, and anti-epileptics) was also recorded at baseline.

3.3 MRI Acquisition and Processing

3.3.1 MRI Acquisition

MRI data were acquired with a 3T whole-body MRI scanner (Siemens Magnetom Trio; Hospital Clinic, Barcelona), using a 32-channel phased array head coil. Structural images

were comprised of conventional high-resolution 3D T1 image [magnetization-prepared rapid-acquisition gradient echo sequence, 208 sagittal slices, repetition time 1970 ms, echo time 2.34 ms, inversion time 1050 ms, flip angle 9°, field of view 25.6 cm, 1 mm isotropic voxel with no gap between slices].

Diffusion-weighted MRI data were acquired using a dual spin-echo DTI sequence with GRAPPA (reduction factor of 4) cardiac gating, with echo time 92 ms. Images were measured using 2 mm isotropic voxels, no gap, 60 axial slices, field of view 23.6 cm. In order to obtain the diffusion tensors, diffusion was measured along 64 non-collinear directions, using a single b-value of 1500 s/mm^2 interleaved with 9 non-diffusion (b = 0) images. To avoid chemical shift artifacts, frequency-selective fat saturation was used to suppress fat signal.

3.3.2 Pre-Processing of T1-Weighted Data (Gray Matter Volume)

Cross-sectional morphometric analysis was conducted using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) in SPM12 (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v17.a, Mathworks, Natick, MA). GM segmentations (unified segmentation algorithm) were used to create a customized DARTEL template. Flow fields were applied to each participant's native GM image. Transformations from customized template to standard space were applied to individual GM segmentations to achieve spatial normalization in Montreal Neurological Institute (MNI) space. Resulting GM normalized images were modulated by their Jacobian determinants and spatially smoothed (FWHM = 8 mm). Total intracranial volume (TIV) was calculated as the sum of GM, WM, and cerebrospinal fluid for each participant.

For longitudinal data, participants' images were acquired in the same scanner at both time points using the same acquisition protocol. Morphometric analysis using the longitudinal processing pipelines was again implemented in the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/) and SPM12 software package (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v17.a; Mathworks, Natick, MA). Specifically, preprocessing for longitudinal data considered the characteristics of intra-subject analysis by the registration of the second image to the baseline image, and a subject-specific mean image was created from the realigned images

and used as a reference for the realignment of both time points. Realigned images were segmented, corrected for signal inhomogeneity, and normalized using the Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL). Then, the corresponding normalization parameters were applied to the segmented GM images of both time points. Resulting GM normalized images were modulated by their Jacobian determinants and spatially smoothed (FWHM = 8 mm), allowing direct comparison of regional differences in GMV (Mechelli et al., 2005). Finally, images were visually inspected.

An explicit absolute masking with a threshold of 0.2 was applied in model selection (i.e., including only those voxels with > 20% probability of being GM) to more selectively distinguish GM boundaries from WM (Ashburner, 2010; James et al., 2014).

3.3.3 Pre-Processing of DTI Data (White Matter Microstructure)

Brain extraction was performed using the FSL Brain Extractor Tool (Smith, 2002). Head motion and eddy-current correction were then performed using the FMRIB's Diffusion Toolbox (FDT) in FMRIB's Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/fdt) and the gradient matrix was rotated (Leemans & Jones, 2009). The diffusion tensor was then reconstructed using Diffusion Toolkit's least-squares estimation algorithm for each voxel provided in Diffusion Toolkit (http://www.trackvis.org/dtk) and its corresponding eigenvalues and eigenvectors were extracted to calculate FA and MD maps.

Fiber orientation distributions were reconstructed using a spherical deconvolution approach based on the damped version of the Richardson-Lucy algorithm (Dell'Acqua et al., 2010) implemented in StarTrack software (http://www.natbrainlab.co.uk). Fiber orientation distribution fields in selected *a priori* fiber crossing regions (splenium of the corpus callosum and corona radiata) were first visualized. Then, a combination of spherical deconvolution parameters was selected to resolve crossing and avoid spurious peaks in GM or cerebral spinal fluid. (See Dell'Acqua et al. (2010), for further details.)

Whole-brain tractography was then performed using a b-spline interpolation of the diffusion tensor field and Euler integration to propagate streamlines following the directions of the principal eigenvector with a step size of 0.5 mm (Basser et al., 2000).

Tractography was started in the different ROIs and was stopped when FA < 0.2 or when the angle between two consecutive tractography steps was larger than 35°. Finally, tractography data and diffusion tensor maps were exported into TrackVis (http://www.trackvis.org) for manual dissection of the tracts.

3.4 Data Analyses

Data analyses were performed in SPSS v.24–25 (SPSS Inc., Chicago, USA), R (v.3.5.1–4.1; R Foundation for Statistical Computing, Vienna, Austria), and MATLAB (MATLAB R2019b, MathWorks, Natick, MA). Specific statistical tests are detailed in the individual studies in *§ Chapters 4 – 7 | Results*. Particularly pertinent aspects of the data analyses of this Doctoral Thesis are provided here as an overview.

The false discovery rate approach was used to correct all *t*-tests and correlations for (q = 0.05). The number of comparisons is specified for each analysis. Both raw *P*-values (*P*) and the *P*-adjusted false discovery rate values (*P*-adj) are reported. Differences were considered statistically significant when *P*-adj ≤ 0.05.

3.4.1 Psychometric Properties and Dimensionality of LARS-s

Test reliability and validity metrics were employed to assess the psychometric properties of the LARS-s. Meanwhile, principal component analysis was implemented to analyze dimensionality, with inclusion of the seven LARS-s variables. Extraction communality values illustrate the estimated variance of each item accounted for by extracted factors.

3.4.2 VBM of T1-Weighted Images

Smoothed GM images were entered into voxel-wise multiple regression models developed in CAT12 to examine the effect of GMV on apathy. TIV, age, education, sex, and CAP were entered into the model as covariates of no interest to control for potential direct or indirect effects on the LARS-s global or subdomain scores. Non-apathetic neuropsychiatric disturbances were included as an additional covariate of no interest when analyzing global apathy with the LARS-s. When examining apathy profiles, an

exploratory threshold was applied. Anatomic and cytoarchitectonic areas were identified using the Automated Anatomical Labeling Atlas included in the xjView toolbox (http://www.alivelearn.net/xjview).

The longitudinal smoothed GMV images were entered into a paired *t*-test to examine the effect of individual-level changes in GMV on changes in apathy between two time points. Time between scans (days), CAP scores, and non-apathetic neuropsychiatric disturbances were entered into the model as covariates of no interest. To test the specificity of the revealed region of atrophy to changes in apathy, the effects of PBA-s depression and UHDRS-cogscore were similarly evaluated through separate paired *t*-tests, including, as an explicit binary mask, the ROI volume in which longitudinal difference in apathy were observed.

3.4.3 Tractography Dissections of DTI Data

Virtual *in vivo* DTI dissections of the three tracts of interest were carried out bilaterally in the native space FA maps and a two-ROI approach (Catani et al., 2002; Catani & Thiebaut de Schotten, 2008; Craig et al., 2009). These include two cortico-striatal tracts, namely the FST and dlPFC-cn, and the cortico-striato-cortical UF. The specific protocols of each dissection are detailed in *§ Chapter 4 | Results: Study 1*. FA and MD values were extracted for analysis of WM microstructure.

3.4.4 Generalized Linear Mixed-Effects Models

In order to study whether vulnerability in a specific ROI was predictive of longitudinal apathy development, as compared with depressive and executive functional outcomes, we implemented generalized linear mixed-effects models.

In the primary set of models, longitudinal PBA-s apathy scores (maximum of six) were the outcome (dependent) variable. Besides time in days (accumulative, from the first to the final visit), the predictor variable of interest was the ROI volume in which we observed longitudinal differences in the VBM analyses. This volume was subsequently extracted from baseline scans using the xjView toolbox (http://www.alivelearn.net/xjview) and MATLAB in-house code (MATLAB R2017a, MathWorks, Natick, MA), and finally adjusted

for TIV at baseline (ROI volume / TIV). Longitudinal values for CAP and nonapathetic neuropsychiatric disturbances were included as control variables.

Details of the analytic strategy, model, and analysis code are detailed in the corresponding study in *§ Chapter 5 | Results: Study 2*. The above framework was identical for models of depression and executive dysfunction, with the exception of the outcome variable (PBA-s depression; UHDRS-cogscore) and neuropsychiatric disturbances variable (non-depressive neuropsychiatric disturbances; total PBA-s score). Lastly, two longitudinal generalized linear mixed-effects models were carried out to evaluate the association between apathy as the outcome variable, the scaled predictor variable being PBA-s depression in the first model and UHDRS-cogscore in the second model.

3.4.5 Disease Trajectories Clustering Analysis

The main objective of the Disease Trajectories clustering analysis was to stratify HD gene-expansion carriers into subgroups that share patterns of longitudinal psychiatric trajectories. To achieve this goal, we implemented an adapted version of the Disease Trajectories unsupervised clustering as recently demonstrated in Giannoula et al. (2024). For context, the Disease Trajectories analysis software utilizes dynamic time warping non-linearly align ('warp') temporal sequences to minimize the accumulated distance between the two trajectories across all points in time. This property renders it well-suited to identify similarities between HD trajectories that may otherwise conceal underlying patterns in psychiatric severity and evolution, without relying on *a priori* models of time.

In brief, the current approach expanded on earlier unsupervised-clustering methodology by incorporating a numerical dimension. This thereby enabled the quantification of individual differences in psychiatric features across the four domains (i.e., depression, irritability, apathy, executive dysfunction) at each point in time across a range of degrees of severity. The Disease Trajectories analysis software assigns a weight (%) to each of the features, in this case the four psychiatric domains, which revealed the contribution of each of the four psychiatric features to a given cluster. Sensitivity analyses were also carried out to assess the performance of the entire clustering methodology in terms of the total averaged heterogeneity (i.e., compactness). For more methodological details, refer to Giannoula et al. (2024) and *§ Chapter 7 | Results: Study 4*.

Chapter 4
Results: Study 1

This study corresponds to:

De Paepe, A. E., Sierpowska, J., Garcia-Gorro, C., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., de Diego-Balaguer, R., & Camara, E. (2019). White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. *NeuroImage: Clinical*, 24, 101965. https://doi.org/10.1016/j.nicl.2019.101965

Chapter 4 | Results: Study 1

White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease

As presented in *§ Chapter 1 | Introduction*, apathy is the neuropsychiatric syndrome that correlates most highly with HD progression. In addition, like early patterns of HD neurodegeneration, apathy is associated with lesions to cortico-striatal connections. However, due to its multidimensional nature and elusive etiology, treatment options for apathy are limited. The objective of this study was thus to disentangle underlying WM microstructural correlates across the apathy spectrum in HD. Forty-six HD individuals (premanifest (N = 22) and manifest (N = 24)) and 35 healthy controls were scanned at 3-tesla and underwent apathy evaluation using the PBA-s and LARS-s, with the latter being characterized into three apathy domains, namely emotional, cognitive, and auto-activation deficit. DTI was used to study whether individual differences in specific cortico-striatal tracts predicted global apathy and its subdomains. An as overview, this study elucidated that apathy profiles may develop along differential timelines, with the auto-activation deficit domain manifesting prior to motor onset. Furthermore, DTI revealed that inter-individual variability in the disruption of discrete cortico-striatal tracts might explain the heterogeneous severity of apathy profiles. Specifically, higher levels of auto-activation deficit symptoms significantly correlated with increased MD in the right UF. Conversely, those with severe cognitive apathy demonstrated increased MD in the right FST and left dlPFC-cn. The current study provides evidence that WM correlates associated with emotional, cognitive, and auto-activation subtypes may elucidate the heterogeneous nature of apathy in HD, as such opening a door for individualized pharmacological management of apathy as a multidimensional syndrome in other neurodegenerative disorders.

4.1 Background

HD is an autosomal dominant, neurodegenerative disorder caused by a CAG polyglutamine expansion in the *HTT* gene (MacDonald et al., 1993). Typically manifesting in mid-adulthood, the disease is characterized by progressive motor and cognitive deficits as well as neuropsychiatric symptoms such as apathy.

Apathy represents one of the most common psychiatric symptoms in HD. Occurring at a prevalence of 52-75% in HD individuals (Paoli et al., 2017), apathy constitutes a significant burden on the quality of life of patients and caregivers. Additionally, apathy have been shown to act as a biomarker of disease progression (Craufurd et al., 2001; Fritz et al., 2018; Kingma et al., 2008; Tabrizi et al., 2013; Thompson et al., 2012; van Duijn et al., 2014). However, other studies using comprehensive psychiatric scales not specific to HD have revealed that many indices increase with disease severity, including depression, anxiety, and obsessive-compulsiveness (Duff et al., 2007) as well as 'frontal' behaviors such as disinhibition and executive dysfunction in addition to apathy (Duff et al., 2010). Nonetheless, an understanding of the expression patterns and potential underlying mechanisms of apathy in HD is essential to clinicians providing care to those impacted by apathy across neurodegenerative disorders.

Apathy is a multidimensional, transdiagnostic syndrome characterized by decreased motivation with a quantitative reduction in goal-directed behaviors. Traditionally, apathy has been associated with cortico-striatal connections, specifically ventral, limbic loops (Bonelli & Cummings, 2007; Delmaire et al., 2013; Tekin & Cummings, 2002; Thompson et al., 2002). This has also been posited in HD populations, where early degeneration has been targeted to cortico-basal ganglia networks (Camacho et al., 2018). However, recent reviews have associated apathy to a wider range of neural substrates specific to three domains: cognitive, emotional, and auto-activation deficit (R. Levy & Dubois, 2006; Pagonabarraga et al., 2015). Cognitive apathy, described as inertia of executive functioning needed to elaborate an objective-oriented behavioral plan (e.g., "I find it difficult to organize future goals"), has been posited to involve the dlPFC and caudate nucleus. On the other hand, emotional apathy is defined as a blunting in affect not attributable to depression (e.g., "I feel indifference for many issues that I was previously

interested in") and relates more closely with lesions to the orbitomedial prefrontal cortex, ACC, amygdala, and ventral striatum. The third domain refers to auto-activation deficit, which translates to difficulties in self-activating thoughts or behavior (e.g., "I need a push to get started on things") (R. Levy & Dubois, 2006; Pagonabarraga et al., 2015). Auto-activation deficit may represent the most severe form of apathy, and is also seen in the form of akinetic mutism, abulia, and Laplane syndrome (Bonelli & Cummings, 2007; Lhermitte et al., 1986). Neurologically, it is encountered in individuals with large frontal and basal ganglia lesions (R. Levy & Dubois, 2006).

Neuroimaging studies using DTI have demonstrated potential for parsing out WM correlates of apathy in HD. Measures such as MD and FA function as proxies to study WM microstructural properties that include not only demyelination accompanying neurodegeneration, but also incipient tissue swelling and redistribution of fluid that occurs at earlier stages of the disease (Sen & Basser, 2005). However, such studies have yielded inconsistent results (Delmaire et al., 2013; Gregory et al., 2015; McColgan et al., 2017), perhaps due to the great variability among HD individuals in the degree and evolution of apathy symptoms. One possible source of individual differences in apathy symptomology could be explained by variability in the degree of neurodegeneration of different neural circuits. In this regard, neuroimaging studies can contribute to the understanding of the neurobiological basis of phenotypic heterogeneity in terms of tract-specific WM microstructure. To date, however, there has been no study investigating the relationship between apathy subtypes and WM connectivity in HD. Disentangling the WM correlates associated with emotional, cognitive, and auto-activation subtypes in HD may elucidate the picture further, clarifying potential profiles of the disease across the apathy spectrum and as such facilitating the diagnosis and treatment of apathy.

Aligning reviews by (Bonelli & Cummings, 2007; R. Levy & Dubois, 2006; Pagonabarraga et al., 2015), we consider apathy as a multidimensional transdiagnostic syndrome that may be represented by WM dysfunction in specific cortico-striatal tracts. First, the FST and the dlPFC-cn are hypothesized to be more involved in cognitive apathy in addition to general apathy. The FST connects the dorsal caudate to the preSMA, a region anatomically and functionally associated with motor preparation as well as non-motor, cognitive tasks (Morris et al., 2016; Nachev et al., 2008). In regard to the dlPFC-cn, the cortical dlPFC

projection is involved predominantly in executive function (Thompson et al., 2002) and emotional regulation (Davidson et al., 2000).

Conversely, the UF is a ventral associative bundle, putatively involved in emotional processing, that connects the anterior temporal lobe with the amygdala and OFC (Catani et al., 2002; Von Der Heide et al., 2013). Indeed, it has recently been shown that changes in GMV in the amygdala and temporal lobe, as well as decreased glucose metabolism in the ACC and ventromedial prefrontal cortex, play a critical role in apathy severity in HD (Martinez-Horta et al., 2018). All such regions constitute the medial orbitofrontal circuit, a cortico-striatal loop that has been directly associated with general apathy (Tekin & Cummings, 2002; Thompson et al., 2002) and which may be involved in emotional apathy.

The last subtype, auto-activation deficit, is associated with more widespread neural correlates. These include terminations of both the FST and UF. With regards to the FST, both the medial superior frontal gyrus and caudate nucleus are cited as anatomical involvements of auto-activation deficit (Pagonabarraga et al., 2015), and the caudate nucleus is associated with planning and execution of self-generated novel action (Monchi et al., 2006). Likewise, the OFC, to which the UF projects, is associated with deficits in auto-activation (R. Levy & Dubois, 2006). Given this evidence, we hypothesize that WM disturbances in the FST or UF may be related with auto-activation deficit.

With regards to global apathy, we utilize an exploratory approach in all three fronto-cortico-striatal tracts, namely the cognitively-oriented FST and dlPFC-cn as well as the limbic UF.

The present exploratory study aims to investigate the neural bases underlying individual differences in both global apathy and its three subtypes in HD. As such, we explored the relationship between apathy and WM microstructure of cortico-striatal connections. To do so, we virtually dissected specific cortico-striatal tracts *in vivo* in order to characterize the FST, dlPFC-cn, and UF. We hypothesized that these discrete cortico-striatal tracts are associated with both global apathy and distinct apathy domains. Specifically, we predicted a positive relationship between WM microstructure disturbance and cognitive apathy in the dorsal, cognitively-associated FST and dlPFC-cn and, comparatively, a positive relationship between emotional apathy and disturbance of the ventrally located UF.

Finally, we predicted that a more severe disruption of the FST and UF tracts would evince a positive association with increased levels of auto-activation deficit.

4.2 Study Design

4.2.1 Participants

Participants' demographics are detailed in **Table 4.1**. Forty-six HD gene-expansion carriers and 35 healthy control participants who matched for age ($t(79) = 0.05$, $P = 0.959$), sex ($t(69.8) = 1.65$, $P = 0.103$), and years of education ($t(78) = -1.31$, $P = 0.194$) participated in this study. Control participant data was utilized in two stages of the analysis: 1) to compare apathy levels and 2) to explore WM microstructure disturbance.

HD individuals were grouped into premanifest ($N = 22$) and manifest ($N = 24$) stages based on their UHDRS diagnostic confidence score for motor abnormalities (Huntington Study Group, 1996).

Table 4.1. Sociodemographic and clinical characteristics of study participants

	Control	Manifest	Premanifest	*P* (Cohen's *d*)
N†	35	24	22	--
Sex (f/m)	18/17	14/10	18/4	0.103
Age (years)	44.00 ± 11	51.00 ± 9.5	36.64 ± 8.7	0.959
Education (years)	12.74 ± 2.7	10.71 ± 2.6	13.29 ± 2.6, *N* = 21	0.194
UHDRS-TMS	--	22.13 ± 12	1.524 ± 3.0, *N* = 21	< 0.001* (2.362)
UHDRS-cogscore	--	183.1 ± 58, *N* = 21	299.1 ± 65, *N* = 19	< 0.001* (1.939)
CAP	--	113.86 ± 18	80.78 ± 16, *N* = 21	< 0.001* (1.956)
TFC	--	11.17 ± 2.0	12.76 ± 0.70, *N* = 21	0.001* (1.066)

Data presented as *mean* ± *standard deviation*. *P*-values refer to independent two-tailed *t* tests between all Huntington's disease gene-expansion carriers combined vs. controls (gray background) and premanifest vs. manifest Huntington's disease gene-expansion carriers (white background). Cohen's *d* is displayed for significant results.
* *P*-values retained significance after false discovery rate correction ($q = 0.05$).
† Number of participants listed in individual cells when differing from this number for each group.
N = number of participants; f = females; m = males; UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score; UHDRS-TMS = Unified Huntington's Disease Rating Scale total motor score (Huntington Study Group, 1996); CAP = standardized age-CAG product (Ross et al., 2014); TFC = Total Functional Capacity.

Despite the fact that HD is clinically diagnosed based on motor onset, pathological changes are often present long before motor symptoms (Martinez-Horta et al., 2016; Thompson et

al., 2012). As such, when examining the association between WM microstructure and apathy subtypes, we studied the disease as a continuum.

Antidepressants are widely used to treat mood disturbances in HD, and tetrabenazine and benzodiazapines are prescribed to manage motor symptoms. However, such medications may worsen apathy severity (S. Frank, 2014). As such, medication use (SSRIs, SARIs, NASSAs, NSRIs, NDRIs, benzodiazapines, tetrabenazines, antipsychotics, and anti-epileptics) was recorded in order to create a binary code delineating the presence or absence of medication at the visit that may affect mood or apathy scores.

Due to time constraints, not all tests were administered to all participants. The specific *N* is detailed for each test. One control and two HD participants did not receive a diffusion-weighted image scan due to claustrophobia. Furthermore, outliers whose Z-scores were greater than |3.5| were excluded. No participants reported previous history of traumatic brain injury or neurological disorder other than HD. The study was approved by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975 and all participants provided written informed consent.

4.2.2 Clinical Evaluation

All HD participants underwent the UHDRS evaluation (Huntington Study Group, 1996), which comprises subscales for motor function (UHDRS-TMS) and cognition (UHDRS-cogscore).

In order to further describe the HD sample, we defined the standardized CAP score for each group, computed as CAP = 100 × age × (CAG – 35.5) / 627 (Ross et al., 2014). In addition, TFC was employed as a measure of independence in daily activities, ranging from thirteen (full capacity) to zero (total incapacity) (Huntington Study Group, 1996). TFC has been shown to be reliable based on radiographic measures of HD progression (Young et al., 1986). All evaluations were carried out by neuropsychologists and psychiatrists specializing in movement disorders.

4.2.3 Neuropsychiatric Assessment

Previous literature has recommended concurrent implementation of multiple apathy questionnaires in order to promote a more consistent evaluation of apathy across studies (Passamonti et al., 2018). As such, we implemented both the PBA-s and the LARS-s. The PBA-s was specifically designed for neuropsychiatric evaluation in HD individuals; however, it cannot be decomposed to measure multiple aspects of apathy, which has been recommended in recent studies (Fritz et al., 2018; Misiura et al., 2019). The comprehensive nature of the LARS-s, in contrast, allows a more in-depth assessment of apathy than that which is available in the PBA-s or other commonly used neuropsychiatric assessments such as the Frontal System Behavior Scale and Neuropsychiatric Inventory (Clarke et al., 2011; Duff et al., 2010; Reijnders et al., 2010), while maintaining applicability for practical and reliable use in everyday clinical practice (Dujardin et al., 2013).

4.2.3.1 Problem Behaviors Assessment, Short-Form

The PBA-s was designed for the evaluation of neuropsychiatric symptoms in HD (Craufurd et al., 2001; Kingma et al., 2008). The PBA-s consists of eleven items, from which three main components measuring apathy, irritability, and affective symptoms have been identified (Callaghan et al., 2015). Following this delineation, we calculated apathy and affective components by summing the corresponding PBA-scores (frequency × severity) of the corresponding items, where 'apathy' is the sum of lack of initiative, perseverative thinking or behavior, and disoriented behavior, and 'affective behavior' is the sum of depressed mood, suicidal ideation, and anxiety. Higher scores indicate more severe/frequent symptoms.

4.2.3.2 Lille Apathy Rating Scale, Short-Form

Global apathy is measured as the total score of the LARS-s (Dujardin et al., 2013; Sockeel et al., 2006). The LARS-s global score ranges from –15 to +15, in which higher scores represent a greater degree of apathy. The cut-off for clinically relevant global apathetic syndromes is defined as a score greater than –7 (Dujardin et al., 2013). We measured apathy domains by combining items into cognitive apathy (everyday productivity, interests), emotional apathy (novelty seeking, emotional responses), and auto-activation

deficit (initiative, motivation). These domains of apathy were categorized based on previous apathy literature (R. Levy & Dubois, 2006; Pagonabarraga et al., 2015; P. H. Robert et al., 2009; Starkstein & Leentjens, 2008).

4.2.4 MRI Data Acquisition

MRI data were acquired through a 3T whole-body MRI scanner (Siemens Magnetom Trio; Hospital Clinic, Barcelona), using a 32-channel phased array head coil. Structural images were comprised of conventional high-resolution 3D T1 image [magnetization-prepared rapid-acquisition gradient echo sequence, 208 sagittal slices, repetition time = 1970 ms, echo time = 2.34 ms, inversion time = 1050 ms, flip angle 9°, field of view = 25.6 cm, 1mm isotropic voxel with no gap between slices].

Diffusion-weighted MRI data were acquired using a dual spin-echo DTI sequence with GRAPPA (reduction factor of 4) cardiac gating, with echo time 92 ms. Images were measured using 2 mm isotropic voxels, no gap, 60 axial slices, field of view 23.6 cm. In order to obtain the diffusion tensors, diffusion was measured along 64 non-collinear directions, using a single b-value of 1500 s/mm^2 interleaved with 9 non-diffusion (b = 0) images. To avoid chemical shift artifacts, frequency-selective fat saturation was used to suppress fat signal.

4.2.5 Diffusion-Weighted MRI Tractography Analysis

4.2.5.1 Preprocessing of DTI Data

Brain extraction was performed using the FSL Brain Extractor Tool (Smith, 2002). Head motion and eddy-current correction were then performed using the FMRIB's Diffusion Toolbox (FDT) in FMRIB's Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/fdt) and the gradient matrix was rotated (Leemans & Jones, 2009). The diffusion tensor was then reconstructed using Diffusion Toolkit's least-squares estimation algorithm for each voxel provided in Diffusion Toolkit (http://www.trackvis.org/dtk) and its corresponding eigenvalues and eigenvectors were extracted to calculate FA and MD maps.

Fiber orientation distributions were reconstructed using a spherical deconvolution approach based on the damped version of the Richardson-Lucy algorithm (Dell'Acqua et

al., 2010) implemented in StarTrack software (http://www.natbrainlab.co.uk). Fiber orientation distribution fields in selected *a priori* fiber crossing regions (splenium of the corpus callosum and corona radiata) were first visualized. Then, a combination of spherical deconvolution parameters was selected to resolve crossing and avoid spurious peaks in GM or cerebral spinal fluid (fixed fiber response corresponding to a shape factor of $\alpha = 2 \times 10–3$ mm^2/s; 200 algorithm iterations, regularization threshold $\eta = 0.04$ and regularization geometric parameter $v = 8$). (See Dell'Acqua et al. (2010), for further details.)

Whole-brain tractography was then performed using a b-spline interpolation of the diffusion tensor field and Euler integration to propagate streamlines following the directions of the principal eigenvector with a step size of 0.5 mm (Basser et al., 2000). Tractography was started in the different regions of interest and was stopped when FA < 0.2 or when the angle between two consecutive tractography steps was larger than 35°. Finally, tractography data and diffusion tensor maps were exported into TrackVis (http://www.trackvis.org) for manual dissection of the tracts.

4.2.5.2 Tractography Dissections

Virtual *in vivo* DTI dissections of the three tracts of interest were carried out bilaterally in the native space FA maps and a two-ROI approach (Catani et al., 2002; Catani & Thiebaut de Schotten, 2008; Craig et al., 2009). These include two cortico-striatal tracts, namely the FST and dlPFC-cn, and the cortico-striato-cortical UF (**Figure 4.1**).

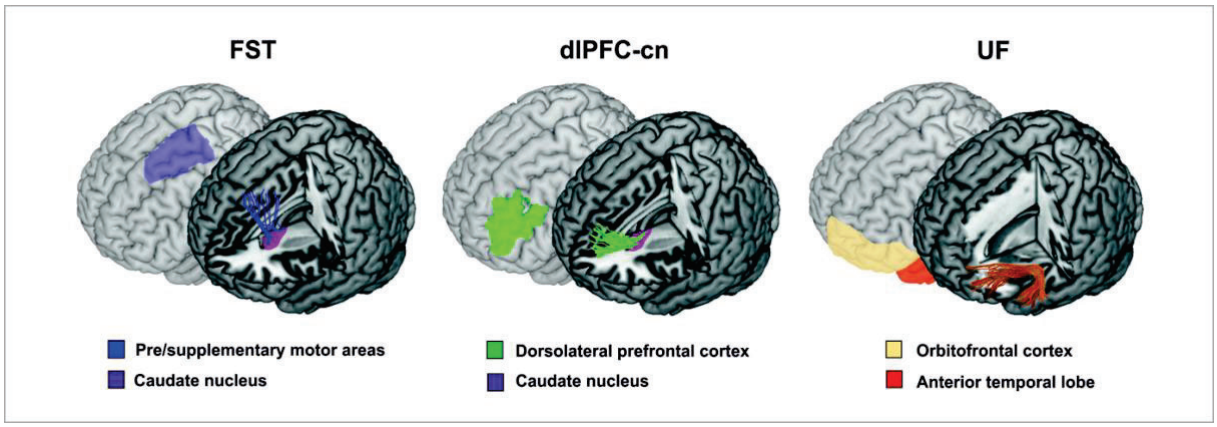


Figure 4.1. Three cortico-striatal tracts of interest. Virtual *in vivo* dissections of frontal cortico-striatal projections for one participant, rendered onto the Montreal Neurological Institute template. Where applicable, tracts are shown projecting to the subcortical region-of-interest (caudate nucleus). Cortical regions of interest are delineated in shadow images, behind. Relevant regions of interest are labeled below

each respective tract. From left to right: FST (frontostriatal tract; pre/supplementary motor areas to caudate nucleus), dlPFC-cn (dorsolateral prefrontal cortex to caudate nucleus tract), and UF (uncinate fasciculus; anterior temporal lobe to orbitofrontal cortex).

To dissect the FST, fibers projecting from the ROI containing the preSMA and SMA, as defined on the axial plane anterior to the hand knob region following anatomical guidelines described by Catani et al. (2012), were restricted to terminate within the caudate nucleus ROI. The caudate nucleus ROIs were segmented by using the FSL FIRST toolbox (Nugent et al., 2013) and then registered to the individual native diffusion space using the FSL FLIRT (Jenkinson & Smith, 2001) and FNIRT (J. L. Andersson et al., 2007) modules after normalizing both the structural T1 images and FA maps.

To dissect the dlPFC-cn, fibers projecting from the dlPFC ROI were restricted to terminate within the caudate nucleus area. The dlPFC ROIs were defined based on (Yi et al., 2016) using the Sallet Dorsal Frontal Connectivity Based Parcellation Atlas Clusters 5, 6, and 7 (Brodmann areas 9/46 dorsal, 9/46 ventral, and 46) in FSL and subsequent transformation to the native FA space for each participant.

To dissect the UF, the ROIs were manually defined on the color FA images of each participant to include WM of the anterior temporal lobe and external capsule, based on previous in-house tractography guidelines (François et al., 2016; Sierpowska et al., 2015).

To blind dissectors to participant identity, controls and patients were randomized. Importantly, due to the presence of marked atrophy in prefrontal regions, the dorsal tracts were unable to be segmented in all patients. Specifically, the FST was not dissected in twelve (four right, four left, four bilaterally) and the dlPFC-cn in ten (one right, seven left, two bilaterally) out of 45 HD individuals with diffusion data. For those participants in which segmentation was possible, FA and MD values were extracted for analysis of WM microstructure.

4.2.6 Statistical Analyses

Statistical analyses were performed in SPSS v.24 (SPSS Inc., Chicago, USA). Independent two-tailed *t* tests and Cohen's *d* were used to describe clinical and sociodemographic differences between groups (J. Cohen, 1977; Lakens, 2013), each surveyed for homogeneity of variance. Pearson's correlations were used to assess associations

between apathy levels, clinical markers, or WM microstructure. In order to study differences in apathy between premanifest, manifest, and control groups, we employed one-way ANOVA with post-hoc comparisons.

Prior to investigating the relationship between structural connectivity and apathy, we examined the level of WM disturbance within each dissected tract of manifest HD patients compared with controls (independent two-tailed *t* tests). Specifically, we examined extracted FA and MD values of the FST, UF, and dlPFC-cn bilaterally. Only those tracts that were affected were further investigated. Lastly, we studied the association between structural connectivity and apathy using Pearson's correlations. When studying global apathy via the PBA-s and LARS-s, we utilized the PBA-s 'affective behavior' component as a covariate of no interest in order to examine apathy as an independent psychiatric syndrome from depression. (For a similar approach, see Martinez-Horta et al. (2016), Misiura et al. (2019), and Reyes et al. (2009).) Similarly, when studying cognitive apathy, UHDRS-cogscore and TFC effects were also controlled.

The false discovery rate approach was used to correct all *t* tests and correlations for multiple comparisons based on the number of tracts tested ($q = 0.05$). The number of comparisons is specified in each analysis. Both raw *P*-values (*P*) and the *P*-adjusted false discovery rate values (*P*-adj) are reported. Differences were considered statistically significant when $P\text{-adj} \leq 0.05$.

4.3 Results

4.3.1 Behavioral Results

Up to 45% of HD gene-expansion carriers demonstrated clinical apathy (PBA-s apathy > 2). HD participants also presented PBA-s scores of > 2 for perseverative phenomena (33%), depressed mood (29%), anxiety (22%), irritability (22%), angry or aggressive behavior (11%), obsessive-compulsive behaviors (11%), delusions/paranoid thinking (6.7%), hallucinations (4.4%), suicidal ideation (4.4%), and disoriented behavior (2.2%). The overall apathy scores of the LARS-s and the PBA-s significantly correlated ($r = 0.33$, $P = 0.038$, $N = 39$), supporting the use of the LARS-s to measure apathy in HD. Furthermore,

the cognitive apathy domain demonstrated a significant negative correlation with both TFC (r = -0.35, P = 0.036, P-adj = 0.049, N = 36) and UHDRS-cogscore (r = -0.46, P = 0.008, P-adj = 0.032, N = 32), while the TFC also presented a significant relationship with the LARS-s (r = -0.48, P = 0.003, P-adj = 0.012, N = 36) and auto-activation deficit (r = -0.35, P = 0.037, P-adj = 0.049, N = 36) (four comparisons; four apathy scales × one clinical measure). As a control analysis, the PBA-s affective behavior sub-score did not show such a relationship with TFC nor UHDRS-cogscore. UHDRS-TMS did not demonstrate a significant correlation with any behavioral markers.

For each scale and subscale, both manifest and premanifest participants presented more severe apathy on average than control participants, with manifest patients demonstrating the most severe apathy. One-way ANOVA demonstrated that these group differences were significant after correction for four comparisons for the global LARS-s ($F(2,66) = 5.12$, P = 0.009, P-adj = 0.018, η_p^2 = 0.134) and auto-activation deficit ($F(2,66) = 5.25$, P = 0.008, P-adj = 0.018, η_p^2 = 0.137), whereas differences in cognitive apathy did not remain significant ($F(2,66) = 3.13$, P = 0.050, P-adj = 0.067 η_p^2 = 0.087) (**Table 4.2; Figure 4.2**). Post-hoc comparisons revealed a significant difference between controls and manifest patients for the global LARS-s (P = 0.002), auto-activation deficit (P = 0.005), and cognitive apathy (P = 0.022). Premanifest participants, however, only significantly differed from controls in the auto-activation deficit domain (P = 0.017) (**Table 4.2; Figure 4.2**), while manifest patients exemplified a tendency toward more severe global apathy and cognitive apathy than premanifest participants (P = 0.070 and P = 0.055, respectively).

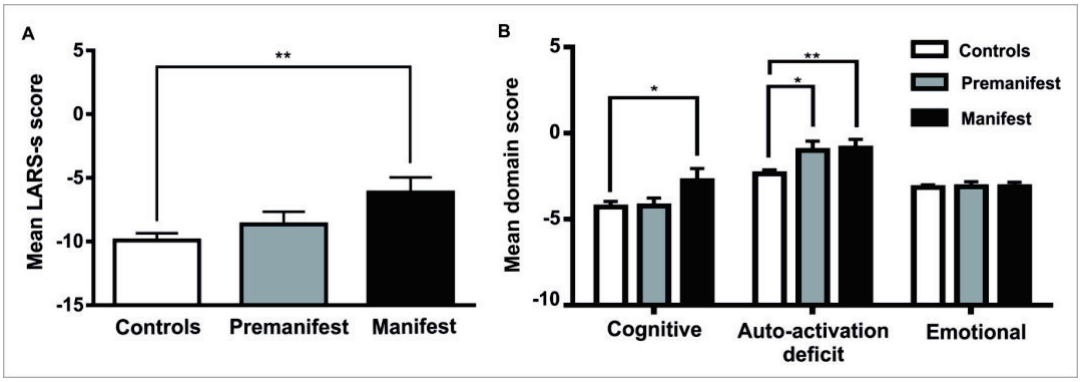


Figure 4.2. Levels of apathy across participant groups. Differences in global apathy (**A**) and three apathy domains (**B**) between controls, premanifest, and manifest Huntington's disease gene-expansion carriers, shown as mean ± standard error of the mean. Global apathy is measured by the short-form Lille Apathy Rating Scale (LARS-s; range -15 to +15), where larger and more positive scores indicate more severe apathy. *P-value < 0.05, **P-value < 0.01 after controlling for multiple comparisons.

Table 4.2. Behavioral results for three participant groups

	Control	Premanifest	Manifest	*P*
LARS-s	-9.90 ± 3.1, *N* = 31	-8.65 ± 4.1, *N* = 17	-6.14 ± 5.4, *N* = 21	0.009*
% clinically relevant§	*12.9%*	*29.4%*	*52.2%*	
Cognitive apathy†	-4.29 ± 1.8	-4.24 ± 1.9	-2.76 ± 3.2	0.050
Auto-activation deficit†	-2.36 ± 1.2	-1.00 ± 2.2	-.86 ± 2.3	0.008*
Emotional apathy†	-3.16 ± 0.90	-3.12 ± 1.2	-2.95 ± 1.3	0.279
PBA-s, apathy‡	--	4.76 ± 8.6, *N* = 21	8.08 ± 7.6, *N* = 24	--
PBA-s, affective‡	--	4.91 ± 5.9	2.63 ± 3.29	--

Data presented as *mean* ± *standard deviation.* Greater or more positive numbers indicate more severe behavioral symptoms. *P*-values refer to one-way ANOVA between controls, premanifest, and manifest groups.
* *P*-values retained significance after false discovery rate correction ($q = 0.05$).
§ Cut-off for clinically relevant global apathetic syndromes is defined as a total LARS-s score > –7 (Dujardin et al., 2013).
† Subscale computed from the LARS-s.
‡ Measured based on 'apathy' and 'affective behavior' components of factor analysis in Callaghan *et al.* (2015).
N = number of participants; LARS-s = Lille Apathy Rating Scale, short-from; PBA-s = Problem Behaviors Assessment, short-form.

Similarly, when manifest and premanifest participants were pooled together, the group maintained significant differences compared to the control group in the global LARS ($t(63.2) = 2.69$, $P = 0.009$, P-adj = 0.018, Cohen's $d = 0.63$) and auto-activation deficit ($t(59.2) = 3.44$, $P = 0.001$, P-adj = 0.004, Cohen's $d = 0.80$). It should be noted that while the premanifest and manifest groups differed in age, this factor could not explain apathy levels across these groups (**Table 4.3**). There were no significant differences in global apathy measures (LARS-s $t(30) = 0.63$, $P = 0.990$), PBA-apathy ($t(34) = 1.25$, $P = 0.261$)), mood scores (PBA-dep ($t(34) = 0.43$, $P = 0.956$)), and apathy subtypes (cognitive apathy ($t(30) = -0.90$, $P = 0.263$), activation deficit ($t(30) = 0.218$, $P = 0.193$)) when comparing HD individuals on or off the specified medications. However, emotional apathy showed a trend that was not significant after multiple comparison correction ($t(78) = 1.82$, $P = 0.015$, P-adj = 0.09, six comparisons; six behavioral measures). Seven HD participants and five controls did not complete the apathy scales. One HD patient did not submit demographic data for years of education.

Table 4.3. Lack of age effect on apathy levels

	Age
LARS-s	0.04 (0.814), *N* = 39
Cognitive apathy†	0.05 (0.774)
Emotional apathy†	0.10 (0.551)
Auto-activation deficit†	-0.97 (0.555)
PBA-s, apathy‡	0.03 (0.843), *N* = 44
PBA-s, affective‡	-0.16 (0.287)

Data presented as *correlation coefficient (P-value)*.
† Subscale computed from the LARS-s.
‡ Measured based on 'apathy' and 'affective behavior' components of factor analysis in (Callaghan et al., 2015).
N = number of participants; LARS-s = Lille Apathy Rating Scale, short-from; PBA-s = Problem Behaviors Assessment, short-form.

4.3.2 Differences in Structural Connectivity for Huntington's Disease Patients and Controls

Manifest HD patients overall showed lower mean FA values and higher mean MD values in the majority of tracts when compared with controls, demonstrating disturbed WM microstructure (**Table 4.4**). Specifically, there was a significant increase in MD values in the right UF ($t(54) = 3.32$, $P = 0.002$, P-adj = 0.006, Cohen's $d = 0.92$), the right FST ($t(47) = 2.77$, $P = 0.008$, P-adj = 0.016, Cohen's $d = 0.82$), and the dlPFC-cn in both the left ($t(38) = 2.21$, $P = 0.033$, P-adj = 0.050, Cohen's $d = 0.72$) and right hemispheres ($t(50) = 5.18$, $P < 0.001$, Cohen's $d = 1.50$) (six comparisons; three tracts × two hemispheres). Post-hoc one-tailed analyses examining differences in structural connectivity between all HD participants and controls replicated these results in three of the four tracts, again in MD values: right dlPFC-cn ($t(68.7) = 3.02$, $P = 0.002$), right UF ($t(74) = 2.27$, $P = 0.013$), and right FST ($t(62) = 1.81$, $P = 0.038$), with the left dlPFC-cn showing a trend ($t(55) = 1.39$, $P = 0.086$).

Table 4.4. Mean FA and MD diffusion values in manifest Huntington's disease patients and controls

			Manifest	*N*	Controls	*N*	Mean Difference (Manifest – Controls)
FST	**Left**	**FA**	0.33569 ± 0.038	20†	0.34830 ± 0.057	30	-0.01261
		MD	0.00074 ± 0.000070	.	0.00070 ± 0.000083	.	0.00004
	Right	**FA**	0.29042 ± 0.082	21†	0.32741 ± 0.055	28	-0.03699
		MD	0.00088 ± 0.00018	.	0.00075 ± 0.00014	.	0.00012*
UF	**Left**	**FA**	0.25435 ± 0.064	23	0.26576 ± 0.067	33	-0.01141
		MD	0.00081 ± 0.00010	.	0.00077 ± 0.000079	.	0.00004
	Right	**FA**	0.26134 ± 0.045	23	0.27424 ± 0.055	33	-0.01290
		MD	0.00074 ± 0.000060	.	0.00070 ± 0.000043	.	0.00004*
dlPFC-cn	**Left**	**FA**	0.35878 ± 0.035	17†	0.36354 ± 0.035	23	-0.00476
		MD	0.00068 ± 0.000036	.	0.00066 ± 0.000035	.	0.00002*
	Right	**FA**	0.37205 ± 0.024	20†	0.37817 ± 0.023	32	-0.00612
		MD	0.00070 ± 0.000031	.	0.00066 ± 0.000025	.	0.00004*

MD values are given in $10^{-3}mm^2/s$ and FA is given as a ratio. FA values were expected to be lower and MD values were expected to be higher in manifest Huntington's disease patients compared with controls.
* *P*-value retained significance after false discovery rate correction at $q = 0.05$.
† Due to the presence of marked atrophy, the FST and dlPFC-cn were unable to be segmented in 4/23 (one right, two left, one bilaterally) and 6/23 (one right, four left, two bilaterally) manifest HD individuals, respectively.
N = number of participants; FA = fractional anisotropy; MD = mean diffusivity; FST = frontostriatal tract; UF = uncinate fasciculus; dlPFC-cn = dorsolateral prefrontal cortex to the caudate nucleus tract.

4.3.3 Association Between Structural Connectivity and Apathy Domains

When examining the association with global apathy, we first employed the PBA-s as an apathy measure in order to more closely parallel previous literature (Delmaire et al., 2013; Gregory et al., 2015). Significant correlations were found between structural connectivity and global apathy in that patients with higher PBA-s apathy values exemplified increased MD in the right FST ($r = 0.46$, $P = 0.005$, P-adj = 0.020, $N = 36$) (four comparisons; four tracts × one apathy scale).

Post-hoc comparisons controlling for CAP, age, and sex maintained significance in the right FST ($r = 0.43$, $P = 0.014$). Further controlling for affective behavior strengthened the relationship in the right FST ($r = 0.67$, $P < 0.001$) and revealed a similar relationship between apathy levels and structural connectivity in the right UF ($r = 0.36$, $P = 0.026$). No

significant correlations were found between global apathy scores and WM connectivity in the dlPFC-cn.

Following these findings, we reproduced these relationships in the right FST and right UF in HD participants using the LARS-s. Specifically, HD individuals with higher LARS-s apathy values exemplified increased MD in both the right FST (r = 0.43, P = 0.014, P-adj = 0.028, N = 33) and the right UF (r = 0.33, P = 0.040, P-adj = 0.040, N = 38) (two comparisons; two tracts × one apathy scale; **Figure 4.3A,B**). We again controlled for CAP, age, and sex, revealing a trend toward significance in the right FST (r = 0.32, P = 0.095). This trend was maintained when additionally controlling for affective behavior in the right FST (r = 0.31, P = 0.106).

In relation to apathy domains, higher cognitive apathy was associated with increases in MD in the left dlPFC-cn (r = 0.38, P = 0.040, P-adj = 0.060, N = 30) and right FST (r = 0.40, P = 0.020, P-adj = 0.060, N = 33) (three comparisons; three cognitive tracts × one apathy scale; **Figure 4.3C,D**). When controlling or CAP, age, and sex, we found that this trend was maintained in both the left dlPFC-cn (r = 0.36, P = 0.071) and right FST (r = 0.34, P = 0.071). Additionally controlling for UHDRS-cogscore and TFC strengthened the relationship in the right FST (r = 0.51, P = 0.010), while removing the association in the left dlPFC-cn.

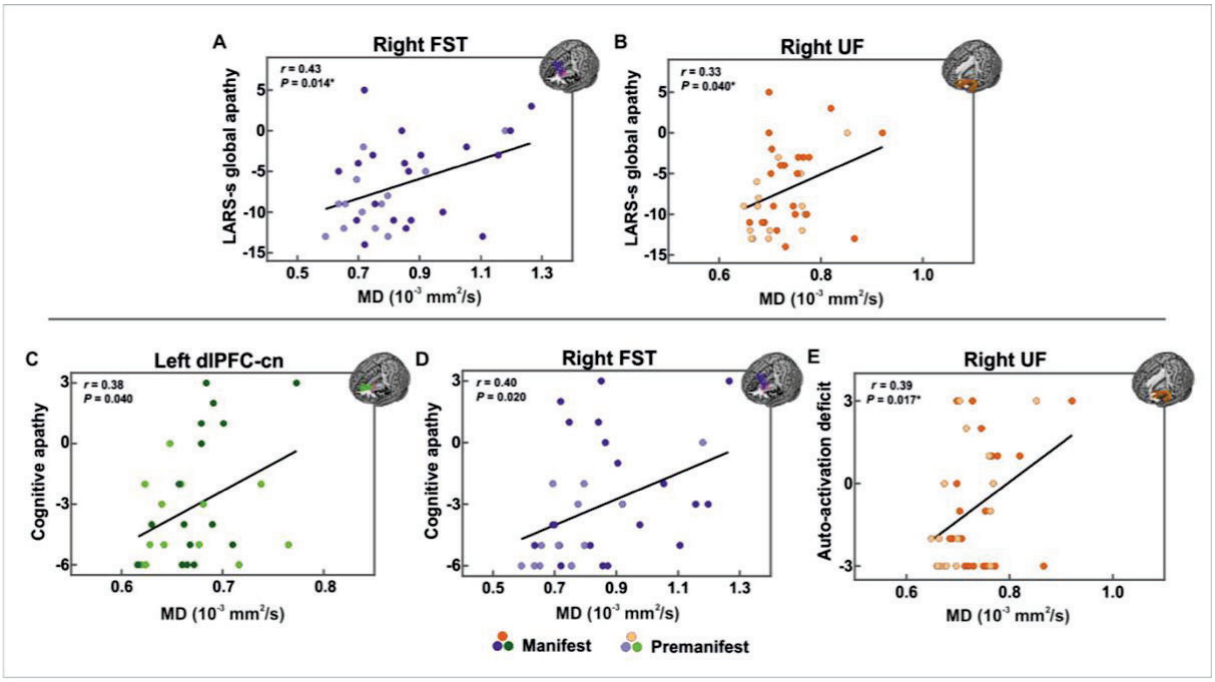


Figure 4.3. Positive relationship between apathy levels and white matter disturbance in the three tracts of interest. Bivariate plot displaying the significant association between global apathy and mean

diffusivity (MD) in the **(A)** right frontostriatal tract (FST) and **(B)** right uncinate fasciculus (UF). Apathy is measured with the short-form Lille Apathy Rating Scale (LARS-s), ranging from -15 to +15, where larger and more positive scores indicate more severe apathy. Larger MD values indicate more severe damage to white matter microstructure. Bivariate plots displaying the associations between apathy domains and the MD of the dorsolateral prefrontal cortex to caudate nucleus tract (dlPFC-cn), FST, and UF, respectively. Cognitive apathy demonstrated a strong association with both the left dlPFC-cn **(C)** and right FST **(D)**, while auto-activation deficit exemplified a significant relationship with the right UF **(E)**. Correlation coefficients (r) and raw P-values (P) for each hemisphere are shown in upper left. Linear regression line is fit for each scatterplot to aid interpretation. *P-value survives false discovery rate correction at $q = 0.05$.

We investigated the relationship between auto-activation deficit and the structural connectivity of both the right FST and right UF. While the FST showed only a trend toward significance in increased right MD ($r = 0.33$, $P = 0.058$, $N = 33$), the UF manifested a strong positive relationship between right MD and the auto-activation deficit score ($r = 0.39$, $P = 0.017$, P-adj = 0.034, $N = 38$), which survived correction for two comparisons (two tracts × one apathy scale; **Figure 4.3E**). Controlling for CAP, age, and sex maintained this association in the right UF ($r = 0.36$, $P = 0.038$), while decreasing the association in the right FST ($r = 0.26$, $P = 0.170$). The UF was not significantly associated with emotional apathy.

Lastly, in order to verify that these correlations were specific to our hypothesized apathy subtypes, we performed control correlations of the dlPFC-cn with auto-activation deficit, both the dlPFC-cn and FST with emotional apathy, and the UF with cognitive apathy. No significant correlations were found.

4.4 Interpretation

The present exploratory study aimed to disentangle the different dimensions of apathy in HD individuals in relation to discrete WM tracts and potential apathy profiles, namely emotional, cognitive, and auto-activation deficit subtypes. In particular, manifest HD patients showed significantly higher levels of global apathy and auto-activation deficit compared with controls, whereas premanifest individuals presented higher levels of auto-activation deficit only. We next hypothesized that inter-individual variability in the disruption of discrete cortico-striatal tracts could explain the differential severity of each apathy profile. Indeed, higher levels of global apathy correlated with a lateralized increased MD in the right FST and right UF. We further revealed that domain-specific

apathy correlated with an increase in MD in the dlPFC-cn and FST for the cognitive domain of apathy and in the UF for auto-activation deficit, also predominantly on the right side.

Overall, we found that increases in apathy were significantly associated with HD progression, as measured by TFC. This finding corroborates the relationship that has consistently been established between increasing apathy and lower TFC (Hamilton et al., 2003; Naarding et al., 2009; Thompson et al., 2002; van Duijn et al., 2014). Such a relationship indicates that apathy may be a suitable biomarker for potentially capturing the spectrum of neurodegeneration.

Affective behavior, however, was not found to correlate with TFC. This supports previous studies showing that, in contrast with apathy, neuropsychiatric symptoms such as anxiety, irritability, and depression do not exhibit a consistent relationship with disease progression or duration, instead manifesting at any stage of the disease progression (Craufurd et al., 2001; Naarding et al., 2009; Thompson et al., 2002) or even showing a reduction over time (Thompson et al., 2012). Secondly, cognitive function, as measured by UHDRS-cogscore, bore a specific relationship with levels of cognitive apathy, but not global apathy.

Compared to controls, both premanifest and manifest groups presented more severe apathy on average. However, it is important to point out that premanifest individuals presented significantly higher levels of auto-activation deficit than controls. This emphasizes the gradual nature of disease onset, which affects neuropsychiatric functioning years or even decades prior to formal disease diagnosis by motor onset (Martinez-Horta et al., 2016; Ross et al., 2014).

Moreover, our findings suggest that specific apathy domains may develop along differential timelines in HD, with auto-activation deficit emerging prior to formal diagnosis. Thus, early in the disease process, difficulty in self-activating thoughts or behavior can signal disease progression. Additionally, levels of cognitive apathy and global apathy were significantly increased in manifest patients when compared with the control group. The fact that significantly higher levels of apathy domains were specific to auto-activation deficit and cognitive apathy supports findings that apathy in HD is

particularly associated with disease evolution in cognitive and functional modalities (Hamilton et al., 2003; Naarding et al., 2009), but not necessarily in motor symptomology.

Regarding the association between MD and apathy subtypes, our findings highlight that damage to WM microstructure in specific tracts may directly contribute to the severity of precise apathy domains in HD. First, those with elevated MD in left dlPFC-cn WM presented higher levels of cognitive apathy. In support of this finding, the GM regions of the dlPFC circuit have been specifically associated with cognitive apathy previously, including cognitive regions of the basal ganglia such as the dorsal caudate in addition to the dlPFC itself (R. Levy & Dubois, 2006; Pagonabarraga et al., 2015).

Second, the right FST also exhibited increased MD in association with higher cognitive apathy levels. To the best of our knowledge and unlike the dlPFC-cn, the cortical terminations of the FST have not yet been cited as being involved in cognitive apathy. Nonetheless, the preSMA shares connections with the dlPFC and, furthermore, is also functionally associated with non-motor, cognitive processing (Morris et al., 2016; Nachev et al., 2008). In addition, preparatory motor regions involved in action anticipation have been found to be associated with the behavioral apathy domain using the LARS (Bonnelle et al., 2016). This proposes the FST as a suitable candidate for involvement in the cognitive form of apathy. Anatomically, cognitive or dorsal territories of the caudate nucleus, to which the FST projects (Riley et al., 2011; J. L. Robinson et al., 2012), are described as being involved in this apathy subtype (R. Levy & Dubois, 2006), and the SMA is specifically referenced as involved in auto-activation deficit (Pagonabarraga et al., 2015) and apathy (Bonnelle et al., 2016). In addition, the preSMA shares a key role in voluntary action (Nachev et al., 2008). Imaging studies report greater (I. H. Jenkins et al., 2000) and earlier (Cunnington et al., 2002) activation in this cortical region when participants perform internally initiated movements in contrast to those generated by external cues and instruction.

Third, heightened MD in the UF also portrayed higher levels of auto-activation deficit, also in the right hemisphere. GM targets of the UF have explicitly been cited as being involved in auto-activation deficit, specifically the ventral ACC, anterior prefrontal cortex, and limbic territories of the basal ganglia including the ventral caudate nucleus (R. Levy & Dubois, 2006). Although its function is rather poorly understood (Catani & Thiebaut de

Schotten, 2008), the UF is often considered a limbic tract involved in emotional processing (Catani et al., 2002; Von Der Heide et al., 2013). However, we did not find a relationship between UF WM and emotional apathy. This suggests that another neural correlate may be more associated with emotional apathy in HD. Alternatively, it is also possible that participants in our sample simply did not present sufficiently high or variable degrees of emotional apathy, as this subtype may affect more advanced stages of the disease.

The fact that only MD was related to apathy severity and disease progression markers suggests that the results may be attributed to atrophy (Steventon et al., 2016) or WM pathology that may be restricted to damage to tissue microstructures, representing different pathophysiological processes, whether due to fiber reorganization, increased membrane permeability, destruction of intracellular compartments, or glial alterations (Acosta-Cabronero et al., 2010; Beaulieu, 2002). Another intriguing result is the rightward bias observed in those tracts that show a significant association with apathy. Of the four associations found between WM and apathy subtypes, three involved the right hemisphere, with only the dlPFC-cn tract showing a left-localized relationship with cognitive apathy. Interestingly, the relationship between apathy and right rather than left hemisphere structural damage has been demonstrated in a number of patient populations, such as in Parkinson's disease (Aarsland et al., 1999; Bogdanova & Cronin-Golomb, 2012), frontotemporal dementia (Mendez et al., 2008; Peters et al., 2006; Zamboni et al., 2008), Alzheimer's disease (Lanctôt et al., 2007), and brain damage patients (S. Andersson et al., 1999) (but see Joseph, 1999; Wager et al., 2003; Roth et al., 2004; Bruen et al., 2008). Tying these results with the rightward trend observed in our paper (both in microstructure effect and its association with apathy), we propose that this rightward bias in WM microstructural abnormalities is an underlying contributor to the prevalent and progressive levels of apathy throughout HD.

Distinct from larger HD networks, our study can take advantage of a tailored methodology, employing specific apathy scales and an optimized DTI protocol in order to study the syndrome precisely and consider the underlying heterogeneity of HD at the individual level. This methodology is currently not available in other studies with HD individuals. However, it should be noted that, while the current analysis aims to elucidate apathy as a syndrome, the PBA-s affective behavior covariate is not capable of teasing out

the full range of depressive symptoms that may confound the evaluation of apathy. Future studies should focus on utilizing more comprehensive neuropsychiatric measures to control for depressive features, and may also consider controlling for obsessive-compulsive behaviors in addition to depressed mood, suicidal ideation, and anxiety. On the other hand, future research may also consider addressing clinically relevant comorbid mental disorders as defined by current diagnostic manuals rather than simply controlling for neuropsychiatric symptoms, a limitation of the present study. Furthermore, while we have attempted to account for the presence or absence of specific medications (including psychotropic drugs), the heterogeneous nature of drug classes and variability in dosage and duration make it difficult to fully explain medication effects that may enhance or engender apathetic symptoms. Lastly, given the small group size, the present study is limited as an exploratory analysis, and replication in a larger independent sample is needed. This is especially important given that DTI data is inherently noisy, potentially resulting in reduced power when detecting abnormalities related to atrophy in WM microstructure. Therefore, further studies need to be carried out in the future using large-scale HD cohorts (TRACK-HD, PREDICT-HD, IMAGE-HD) in order to better understand the neural correlates involved in the spectrum of apathy.

The present findings are highly relevant in corroborating the progressive nature of apathy as a biomarker in HD while also pioneering research on the disentanglement of apathy profiles in HD. As such, these results bear implications for a differential diagnosis of apathy subtypes and, subsequently, more individualized pharmacological management. For example, cholinesterase inhibitors (which increase acetylcholine levels) or cholinergic precursors has been shown to improve cognitive performance and thus may be preferred in the treatment of cognitive apathy, while methylphenidate (which increases levels of catecholamines) or dopaminergic agonists may be reserved for behavioral aspects of apathy in HD (Nobis & Husain, 2018), such as auto-activation deficit. As a whole, this research contributes to the elucidation of potential profiles of HD, which is currently diagnosed solely as a progressive movement disorder (Rosas et al., 2008), yet whose patients would benefit from profile development due to the heterogeneous nature of symptom presentation and patterns of degeneration (Friedman et al., 2005; Georgiou et al., 1999; Gómez-Esteban et al., 2007; Thu et al., 2010; Tippett et al., 2007).

Chapter 5
Results: Study 2

This study corresponds to:

De Paepe, A. E., Ara, A., Garcia-Gorro, C., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., Diego-Balaguer, R. de, & Camara, E. (2021). Gray Matter Vulnerabilities Predict Longitudinal Development of Apathy in Huntington's Disease. *Movement Disorders*, 36(5). https://doi.org/10.1002/mds.28638

Chapter 5 | Results: Study 2

Gray matter vulnerabilities predict longitudinal development of apathy in Huntington's disease

Apathy, a common neuropsychiatric disturbance in HD, is sub-served by a complex neurobiological network. However, no study has yet employed a whole-brain approach to examine underlying regional vulnerabilities that may precipitate apathy changes over time. The objective of this study was thus to identify whole-brain GMV vulnerabilities that may predict longitudinal apathy development in HD. Forty-five HD individuals (31 female) were scanned and evaluated for apathy and other neuropsychiatric features using the PBA-s for a maximum total of six longitudinal visits (including baseline). In order to identify regions where changes in GMV may describe changes in apathy, we performed longitudinal VBM on those 33 participants with an MRI scan on their second visit at 18 ± 6mon follow-up (78 MRI datasets). We next employed a generalized linear mixed-effects model (N = 45) to elucidate whether initial and specific GMV may predict apathy development over time. Utilizing longitudinal VBM, this study revealed a relationship between increases in apathy and specific GMV atrophy in the right MCC. Furthermore, vulnerability in the right MCC volume at baseline successfully predicted the severity and progression of apathy over time. Overall, this study highlights that individual differences in apathy in HD may be explained by variability in atrophy and initial vulnerabilities in the right MCC, a region implicated in action-initiation. These findings thus serve to facilitate the prediction of an apathetic profile, permitting targeted, time-sensitive interventions in neurodegenerative disease with potential implications in otherwise healthy populations.

5.1 Background

HD is an inherited neurodegenerative disorder that typically manifests in mid-adulthood and is caused by a CAG polyglutamine expansion in the *HTT* gene (Langbehn et al., 2010; MacDonald et al., 1993). GM loss begins in the neostriatum before extending into the cingulate, pre-central and prefrontal regions as well as occipital, parietal, and temporal cortices (Tabrizi et al., 2009; Waldvogel et al., 2014), with the rate of atrophy being most pronounced in the basal ganglia (Tabrizi et al., 2013). This widespread degeneration results in a triad of progressive symptoms, including motor dysfunction, cognitive deficits, and neuropsychiatric disturbances such as apathy.

Apathy represents the most common neuropsychiatric feature in HD, occurring at a prevalence of 46-76% across premanifest and manifest HD individuals (Camacho et al., 2018). As such, apathy constitutes a significant burden on the quality of life of patients and caregivers (Chase, 2011; Paoli et al., 2017), impacting autonomy and social life. Additionally, unlike other common neuropsychiatric signs in HD, such as depression (Naarding et al., 2009; Thompson et al., 2012), apathy has been shown to closely track disease progression in cognitive and functional decline (Baake, Coppen, et al., 2018; Kingma et al., 2008; Tabrizi et al., 2013; Thompson et al., 2002; van Duijn et al., 2014), although this positive coupling is not always reported (Mason & Barker, 2015; van Duijn et al., 2013).

When considering the underlying brain correlates of apathy in HD, recent studies have revealed that apathy is sub-served by a complex organization of subcortical and cortical regions that span cognitive and limbic territories. In particular, higher apathy severity has been associated with widespread neurobiological changes across imaging modalities, including GMV atrophy (Martinez-Horta et al., 2018), reduced functional connectivity (McColgan et al., 2017), and impaired WM microstructure (De Paepe et al., 2019; Delmaire et al., 2013). While such cross-sectional studies shed light on potential therapeutic targets for apathy in HD, their applicability in delineating longitudinal changes in a progressive neurodegenerative disorder is limited.

However, despite this need, few current studies examine the development of apathy in HD over time. Meanwhile, those longitudinal studies that do exist investigate the

evolution of neuropsychiatric symptoms (Mason & Barker, 2015; Paulsen et al., 2005; Tabrizi et al., 2013; Thompson et al., 2012; van Duijn et al., 2013) in absence of neuroimaging data, or focus on an ROI based on *a priori* hypotheses of limited scope (Baake, Coppen, et al., 2018). It is therefore of crucial importance to conduct longitudinal analyses at the whole-brain level in order to establish whether atrophy across subcortical and cortical levels may predate, and thereby predict, apathy presentation. These specific patterns of brain alterations may, in turn, serve as targeted biomarkers that discern which individuals may be more susceptible to develop into a more neuropsychiatric clinical profile as the disease progresses (Garcia-Gorro et al., 2019). Such individual-level differentiation of disease profiles would thus provide an opportunity for early interventions that take advantage of a more personalized preventive and treatment regimen.

The goal of the present study is thus to examine the relationship between intra-individual changes in GMV and apathy, as opposed to depression and executive dysfunction, across the continuum of HD. Specifically, we performed longitudinal VBM at the whole-brain level in order to identify regions where GMV atrophy may describe changes in apathy severity across two time points. We hypothesized that a greater loss of GMV would be associated with a larger increase in apathy severity over time. Subsequently, we employed a generalized linear mixed-effects model in order to elucidate whether initial and specific GMV vulnerability would successfully predict the longitudinal development of apathy at the individual level. We expected that regional vulnerability (lower initial volumes) would be associated with higher rates of apathy presentation over time.

5.2 Study Design

5.2.1 Participants

Participants' sociodemographic and clinical data are detailed in **Table 5.1**. Forty-five HD individuals underwent neuroimaging and apathy evaluation using the PBA-s at baseline (Callaghan et al., 2015). While HD is clinically diagnosed based on motor onset, pathological, cognitive, and neuropsychiatric changes are often present long before motor symptoms (Martinez-Horta et al., 2016; Thompson et al., 2012). As such, and due to the

fact that our main target was the neuropsychiatric profile, we studied the disease as a continuum. Therefore, while not all participants displayed motor symptoms (**Table 5.1**), each was genetically confirmed as a HD gene-carrier (43.91 ± 3.04 CAG repeats).

Table 5.1. Sociodemographic information at baseline

	Pre-HD	Manifest HD	HD all
N	22	23	45
Sex (f/m)	18/4	13/10	31/14
Age (years)	38.32 ± 9.2	52.48 ± 10.1	45.56 ± 11.9
Education (years)	13.95 ± 2.9	10.74 ± 2.9	12.31 ± 3.3
CAP	82.89 ± 19.2	113.14 ± 19.2	98.35 ± 24.4
UHDRS-TMS	2.00 ± 3.7	22.57 ± 12.6	12.51 ± 13.9
UHDRS-cogscore	292.77 ± 62.4	183.14 ± 58.0, *N* = 21	239.23 ± 81.4, *N* = 43
TFC	12.79 ± 0.7, *N* = 19	11.26 ± 2.0	11.95 ± 1.7, *N* = 42
PBA-s total	12.50 ± 18.7	18.04 ± 17.6	15.33 ± 18.1
Apathy	2.55 ± 4.3	5.61 ± 5.0	4.11 ± 4.9
Perseveration	2.45 ± 4.4	2.96 ± 3.3	2.71 ± 3.8
Depressed mood	2.45 ± 3.5	1.70 ± 2.7	2.07 ± 3.1
Irritability	1.00 ± 2.2	2.70 ± 3.7	1.87 ± 3.2
Anxiety	1.41 ± 2.2	1.57 ± 2.8	1.49 ± 2.5
Paranoia	1.09 ± 3.5	0.57 ± 2.5	0.82 ± 3.0
Anger/aggression	0.41 ± 1.7	0.91 ± 2.0	0.67 ±1.8
Obsessive-compulsive	0.18 ± 0.9	1.04 ± 2.8	0.62 ± 2.1
Hallucinations	0.23 ± 0.9	0.52 ± 2.5	0.38 ± 1.9
Suicidal ideation	0.68 ± 1.8	0.09 ± 0.3	0.38 ± 1.3
Disorientation	0.05 ± 0.2	0.39 ± 0.9	0.22 ± 0.7

Data presented as *mean* ± *standard deviation*. *N* (number of participants) detailed in individual cells where differing. Premanifest and manifest participants grouped based on their Unified Huntington's Disease Rating Scale diagnostic confidence score for motor abnormalities at the first visit (Huntington Study Group, 1996).
CAP = standardized age-CAG product (Ross et al., 2014); f = females; HD = Huntington's disease; m = males; PBA-s = short-Problem Behaviors Assessment; Pre-HD = premanifest; TFC = Total Functional Capacity; UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score (Huntington Study Group, 1996); UHDRS-TMS = Unified Huntington's Disease Rating Scale total motor score (Huntington Study Group, 1996).

In addition to the first (baseline) scan and assessment, all participants received neuropsychiatric evaluation using the PBA-s over a maximum total of six longitudinal visits (including baseline). Thirty-three participants also received an MRI scan on their second visit at 18 ± 6 months follow-up. The generalized linear mixed-effects model analysis included all participants (*N* = 45), with a mean number of 3.69 ± 1.5 assessments and mean inter-assessment duration of 13.5 ± 2 months.

No participants reported previous history of neurological disorder other than HD. The study was approved by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975, and all participants provided written informed consent.

5.2.2 Clinical evaluation

The evaluation of neuropsychiatric symptoms was conducted using the PBA-s, a semi-structured interview, administered in the presence of the main caregiver or other knowledgeable informant, which consists of eleven items: depressed mood, suicidal ideation, anxiety, irritability, angry or aggressive behavior, lack of initiative (apathy), preservative thinking or behavior, obsessive-compulsive behavior, paranoid/delusional thinking or behavior, hallucinations, and disoriented behavior. Scores are calculated as the product of frequency × severity (range: 0 to 16) for each symptom. An apathy score > 2 was considered clinically relevant (Martinez-Horta et al., 2016). As a control variable, non-apathetic neuropsychiatric disturbances were calculated as the sum of all ten additional (non-apathetic) items, allowing the examination of apathy as an independent neuropsychiatric symptom from the others. Similarly, non-depressive neuropsychiatric disturbances (all but depressed mood, suicidal ideation, and anxiety (Craufurd et al., 2001; Tabrizi et al., 2009)) and the total PBA-s score were taken into account in models of depression and executive dysfunction, respectively.

In addition to the PBA-s, all participants were assessed with the UDHRS (Huntington Study Group, 1996) for motor (UHDRS-TMS) and executive function (UHDRS-cogscore). UHDRS-TMS assesses the motor features of dysarthria, chorea, dystonia, gait, postural stability, and oculomotor function. UHDRS-cogscore includes the F-A-S test (phonetic verbal fluency) and the Symbol Digit Modalities Test (psychomotor speed) as well as the word-reading, color-naming, and interference components of the Stroop Test (processing speed, attention, and inhibitory control). A lower UHDRS-cogscore, in contrast to higher UHDRS-TMS and PBA-s scores, represents worse functioning. TFC was employed as a measure of independence in daily activities (range: 0 (total incapacity) to 13 (full capacity)). Lastly, the standardized CAP score, computed as CAP = 100 × age × (CAG – 35.5) / 627, was used as a measurement of HD state (Ross et al., 2014). All clinical assessments were carried out by neurologists or neuropsychologists specializing in movement disorders.

5.2.3 MRI Acquisition and Processing

MRI data were acquired through a 3T whole-body MRI scanner (Siemens Magnetom Trio; Hospital Clinic, Barcelona), using a 32-channel phased array head coil. Participants' images were acquired in the same scanner at both time points using the same acquisition protocol. Specifically, structural images comprised a conventional high-resolution 3D T1 image (magnetization-prepared rapid-acquisition gradient echo sequence), 208 sagittal slices, repetition time = 1970 ms, echo time = 2.34 ms, inversion time = 1050 ms, flip angle = 9°, field of view = 256 mm, 1 mm isotropic voxel with no gap between slices.

5.2.4 Data analysis

5.2.4.1 Sociodemographic and Clinical Data

Statistical analyses of group demographics were performed in SPSS (v.25, SPSS Inc., Chicago, USA). In order to evaluate the potential of apathy to relate with HD state, we used univariate Spearman correlations of PBA-s apathy scores with CAP at baseline.

5.2.4.2 VBM of T1-Weighted Images

We carried out morphometric analysis using the longitudinal processing pipelines implemented in CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/) and SPM12 software package (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v17.a, Mathworks, Natick, MA).

Specifically, preprocessing for the longitudinal data considered the characteristics of intra-subject analysis by the registration of the second image to the baseline image, and a subject-specific mean image was created from the realigned images and used as a reference for the realignment of both time points. Realigned images were segmented, corrected for signal inhomogeneity and normalized using the Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL). Then, the corresponding normalization parameters were applied to the segmented GM images of both time points. Resulting GM normalized images were modulated by their Jacobian determinants and spatially smoothed (FWHM = 8mm), allowing direct comparison of

regional differences in GMV (Mechelli et al., 2005). Finally, images were visually inspected.

The longitudinal smoothed GMV images were entered into a paired t-test in order to examine the effect of individual-level changes in GMV on changes in apathy between two time points. Time between scans (days), CAP scores, and non-apathetic neuropsychiatric disturbances were entered into the model as covariates of no interest. Explicit absolute masking with a threshold of 0.2 was applied in model selection (i.e., including only voxels with > 20% probability of being GM) to more selectively distinguish GMV boundaries (Ashburner, 2010; James et al., 2014). Significant results were identified at $P < 0.001$ (uncorrected) and a threshold of $P < 0.05$ applied at cluster-level, with a minimum cluster size of 100 contiguous voxels. To test the specificity of the revealed region of atrophy to changes in apathy, the effects of PBA-s depression and UHDRS-cogscore were similarly evaluated through separate paired t-tests, including, as an explicit binary mask, the ROI volume in which we observed longitudinal difference in apathy.

As exploratory analysis, we carried out additional cross-sectional morphometric analysis using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) in the SPM12 software package (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v17.a, Mathworks, Natick, MA) for all participants ($N = 45$).

Specifically, unified segmentation (Ashburner & Friston, 2005) was applied to the structural T1-weighted images of each subject to estimate tissue GM probability maps, which were then normalized to a standard stereotactic space using the corresponding DARTEL transformations (Ashburner, 2007) to achieve spatial normalization in MNI space (Ashburner & Friston, 2009). The resulting GM normalized images were modulated by their Jacobian determinants and spatially smoothed using an 8mm FWHM surface-based smoothing kernel. Finally, images were visually inspected.

The TIV was calculated as the sum of GM, WM, and cerebrospinal fluid, averaged across both sessions.

The smoothed GMV images were entered into a voxel-wise multiple regression in order to examine the effect of GMV on apathy. TIV, age, education, sex, CAP scores, and non-apathetic neuropsychiatric disturbances, as measured by the PBA-s, were entered into the

model as covariates of no interest. The non-apathetic neuropsychiatric component was the sum of all ten additional (non-apathetic) neuropsychiatric factors evaluated with the PBA-s, allowing the examination of apathy as an independent neuropsychiatric symptom from the others. An explicit absolute masking with a threshold of 0.2 was applied in model selection (i.e., exclusively including voxels with > 20% probability of being GM) to more selectively distinguish GM boundaries (Ashburner, 2010; James et al., 2014). For illustrative purposes, significant results were identified at three discrete significance levels (uncorrected) applied at voxel-level, with a minimum cluster size of 100 contiguous voxels: $P < 0.05$, $P < 0.01$, $P < 0.005$.

5.2.4.3 Generalized Linear Mixed-Effects Models

In order to study whether vulnerability in a specific ROI was predictive of longitudinal apathy development, as compared with depressive and executive functional outcomes, we implemented generalized linear mixed-effects models in R (v.3.5.1, R Foundation for Statistical Computing, Vienna, Austria). Generalized linear mixed-effects models provide greater flexibility in longitudinal analysis and are well suited for patient populations, as they allow for a different number of observations for each subject and non-equal intervals between assessments (Gibbons et al., 2010). Such models have previously been implemented in the study of HD (Bonner-Jackson et al., 2013; de Diego-Balaguer et al., 2016; Harrington et al., 2016; Odish et al., 2015).

In the primary set of models, longitudinal PBA-s apathy scores (maximum of six) were the outcome (dependent) variable. Besides time in days (accumulative, from the first to the final visit), the predictor variable of interest was the ROI volume in which we observed longitudinal differences in the VBM analyses. This volume was subsequently extracted from baseline scans using the xjView toolbox (http://www.alivelearn.net/xjview) and MATLAB in-house code (MATLAB R2017a, MathWorks, Natick, MA), and finally adjusted for TIV at baseline [ROI volume / TIV]. Longitudinal values for CAP and non-apathetic neuropsychiatric disturbances were included as control variables. Because apathy scores are operationalized as counts, the dependent variable was assumed to follow a Poisson distribution, with the logarithmic link function used to map out predictions. Subject-specific random effects were specified for baseline (intercept), and random slopes were modeled for time. Predictor and control variables were scaled using the *scale* function in

R (Becker et al., 1988). In order to improve the precision of intercept estimates, all participants were included in analyses.

The analytic strategy was to fit two models for the outcome variable of longitudinal apathy. Model 1.0, the null model, only included the predictor variable of time. Meanwhile, Model 1.1 additionally included baseline ROI volume, with an interaction term between baseline ROI volume and time (see Equation 1). In both models, scaled predictor and control variables satisfied the condition for low multicollinearity, possessing a variance inflation factor < 2 as determined by the *check_collinearity* function in R (Lüdecke et al., 2019).

Model 1.1, the more complex of the two models, is explicitly defined for clarity. Suppose the outcome variable, longitudinal apathy, is denoted as y, time as t, the initial ROI volume as r, CAP as c, non-apathetic neuropsychiatric disturbances as p, and s as the subject. The statistical model can then be defined as

$$y = \boldsymbol{\alpha} + \beta_1 t + \beta_2 r + \beta_3(t)(r) + \beta_4 c + \beta_5 p + e_s \quad (1)$$

where $\boldsymbol{\alpha}$ is the intercept, β_1 and β_2 are the main effects, β_3 are the effects of the interaction term between time and the ROI volume, β_4 and β_5 are the respective slope effects of the control covariates, and e_s is subject-specific random effects at the intercept.

Goodness of fit of the two models was evaluated using the likelihood ratio test along with a probability scaling of Akaike's information criteria weight (W). The criteria represent the relative likelihood, or quality, of the statistical model. W values are considered a global relative effect size measure (Burnham & Anderson, 2002; Long, 2011) and range from 0 to 1 (closer to 1 indicating better relative fit).

The above framework was identical for models of depression (Model 2.0 and 2.1) and executive dysfunction (Model 3.0 and 3.1), with the exception of the outcome variable (PBA-s depression; UHDRS-cogscore) and neuropsychiatric disturbances variable (non-depressive neuropsychiatric disturbances; total PBA-s score). Lastly, two longitudinal generalized linear mixed-effects models were carried out to evaluate the association between apathy as the outcome variable, the scaled predictor variable being PBA-s depression in the first model and UHDRS-cogscore in the second model.

Due to the lack of apathy signs in twelve individuals (26.7%), we utilized the glmmTMB package to account for zero-inflation in the set of apathy models (Brooks et al., 2017), where its application was statistically significant ($P_{zi} < 0.05$), but not in models with outcome variables of depression and executive dysfunction. Zero-inflated models are designed to accommodate samples with a large number of zeros, in such a way that predictions are made considering the expected number of zeros under the current statistical process. Analysis code is available in *§ 5.5 Supplemental Information* at the end of this Chapter.

5.3 Results

5.3.1 Sociodemographic and Clinical Data

At the first (baseline) visit, PBA-s apathy levels ranged from 0 to 16, with an average of 4.28 ± 5.0, with 47.8% of individuals manifesting clinical levels of apathy and 41.3% of individuals not expressing signs of apathy. Baseline apathy scores were found to significantly correlate with CAP ($r_s = 0.381$, $P = 0.010$, $N = 45$), with a large effect size (Gignac & Szodorai, 2016). When considering longitudinal data, 64.4% of individuals manifested clinical levels of apathy at some point throughout the course of the study, with only 26.7% not expressing even mild signs of apathy. Baseline characteristics of the VBM analysis are displayed in **Table 5.2**. Longitudinal data from each participant are depicted in **Figure 5.1**.

Table 5.2. Sociodemographic information for longitudinal VBM cohort (at baseline)

	Pre-HD	Manifest HD	HD all
N	15	18	33
Sex (f/m)	14/1	9/9	23/10
Age (years)	41.13 ± 9.4	50.78 ± 10.0	46.39 ± 10.8
Education (years)	14.07 ± 2.8	10.83 ± 2.8	12.30 ± 3.2
CAP	86.27 ± 22	109.87 ± 17, *N* = 16	99.14 ± 22.6
UHDRS-TMS	2.07 ± 3.8	18.44 ± 8.2	11.00 ± 10.5
UHDRS-cogscore	256.33 ± 54	164.50 ± 41, *N* = 16	208.94 ± 66, *N* = 31
TFC	12.92 ± 0.29, *N* = 12	11.50 ± 1.5	12.07 ± 1.4
PBA-s total	10.47 ± 18	12.56 ± 12	11.61 ± 15
Apathy	2.40 ± 4.4	4.17 ± 4.4	3.36 ± 4.4
Perseveration	2.40 ± 4.5	2.22 ± 2.8	2.30 ± 3.6
Depressed mood	2.20 ± 3.4	1.06 ± 1.8	1.58 ± 2.7
Irritability	0.93 ± 2.3	2.56 ± 3.9	1.82 ± 3.3
Anxiety	1.00 ± 2.1	0.78 ± 1.3	0.88 ± 1.7
Paranoia	0.27 ± 1.0	0.06 ± 0.24	0.15 ± 0.71
Anger/aggression	0.53 ± 2.1	0.39 ± 1.4	0.46 ± 1.7
Obsessive-compulsive	0.27 ± 1.0	1.00 ± 2.9	0.67 ± 2.3
Hallucinations	0.07 ± 0.26	0.00 ± 0.00	0.03 ± 0.17
Suicidal ideation	0.40 ± 1.5	0.11 ± 0.32	0.24 ± 1.1
Disorientation	0.00 ± 0.00	0.22 ± 0.55	0.12 ± 0.42

Data presented as *mean* ± *standard deviation*. *N* (number of participants) detailed in individual cells where differing. Premanifest and manifest participants grouped based on their Unified Huntington's Disease Rating Scale diagnostic confidence score for motor abnormalities at the first visit (Huntington Study Group, 1996).
CAP = standardized age-CAG product (Ross et al., 2014); f = females; HD = Huntington's disease; m = males; PBA-s = Problem Behaviors Assessment, short-form (Callaghan et al., 2015); Pre-HD = premanifest; TFC = Total Functional Capacity; UHDRS-TMS = Unified Huntington's Disease Rating Scale total motor score (Huntington Study Group, 1996); UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score (Huntington Study Group, 1996); VBM = voxel-based morphometry.

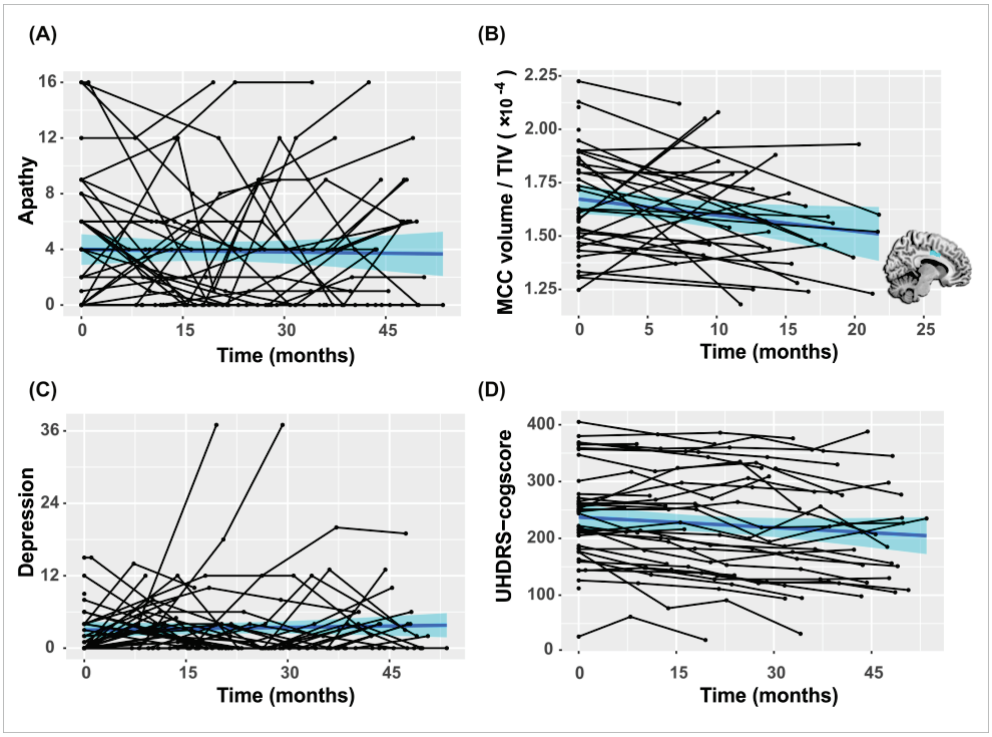


Figure 5.1. Raw longitudinal data for each participant, illustrating apathy **(A),** TIV-adjusted MCC volume **(B)**, depression **(C)**, and cognition **(D).** Fitted linear regression models with respective 95% confidence

intervals presented in blue. Mask of MCC volume inlaid. MCC = middle cingulate cortex; TIV = total intracranial volume.

5.3.2 VBM Results

We first sought to examine the relationship between intra-individual changes in apathy severity and changes in GMV across two time points. Utilizing a whole-brain approach, we found that an increase in apathy was associated with a larger reduction in GMV specifically in the right MCC (BA 24) (**Figure 5.2**). This relationship maintained significance both with (*cluster size* = 259, $T = 4.63$, $P < 0.001$, MNI [$x = 9, y = 8, z = 35$]) and without (*cluster size* = 286, $T = 4.50$, $P < 0.001$, MNI [$x = 14, y = 2, z = 41$]) controlling the CAP score as a proxy measure for disease state after correction for multiple comparisons at cluster-level. In *post-hoc* analysis controlling for non-apathetic neuropsychiatric disturbances, small volume correction (sphere radius = 12mm; $P = 0.005$) centered on the right MCC showed the ROI to maintain the direction of the effect ($T = 2.89$, $P = 0.004$, MNI [$x = 9, y = 9, z = 33$]). Furthermore, this right MCC effect was maintained at whole-brain level when assessed in premanifest ($N = 15$) individuals only (*cluster size* = 320, $T = 4.89$, $P < 0.001$, MNI [$x = 8, y = 5, z = 30$]), in addition to the cuneus and inferior occipital lobe (**Table 5.3**). Meanwhile, no significant effects were found in separate control analyses between the right MCC with depression and UHDRS-cogscore, when assessed with the ROI mask across all HD participants.

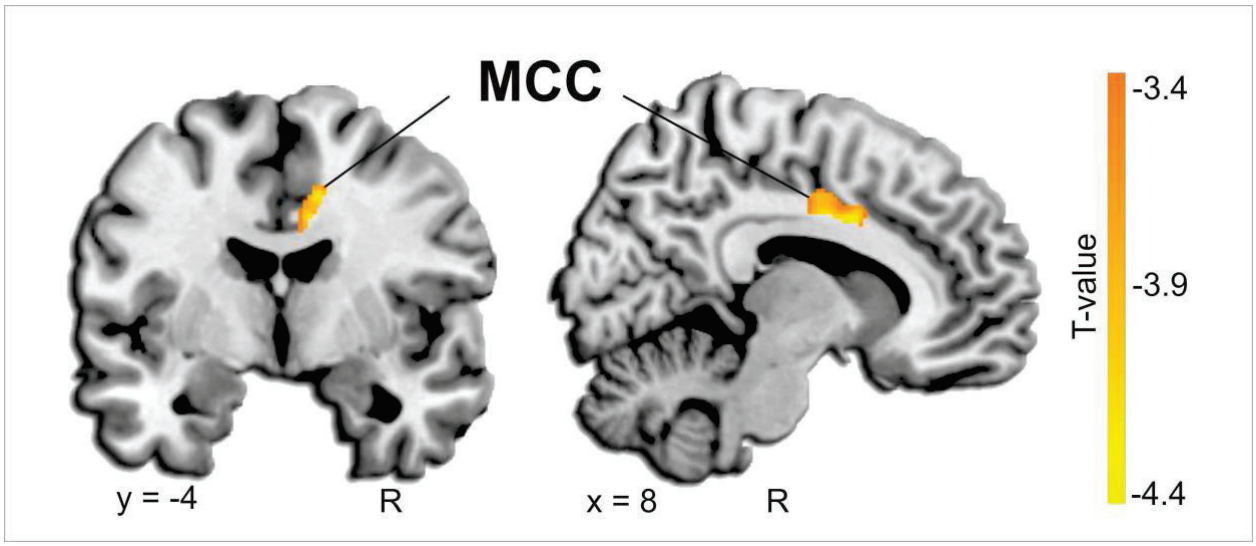


Figure 5.2. Specific gray matter atrophy in the right MCC relates with increasing apathy severity over time (18 ± 6mon follow-up; cluster size = 100; $P < 0.001$). Slice position labeled in Montreal Neurological Institute coordinates. MCC = middle cingulate cortex; R = right.

Table 5.3. Longitudinal VBM of GMV and PBA-s apathy in premanifest HD individuals

Anatomical region	Cluster size	T value	*P* value	MNI Coordinates (*x,y,z*)
Premanifest HD				
L Cuneus	879	5.31	< 0.001	-5 -95 18
R Inferior occipital lobe	948	5.09	< 0.001	38 -87 5
R MCC	320	4.89	< 0.001	8 5 30

P values were significant at $P < 0.005$ (uncorrected) and a threshold of $P < 0.05$ applied at cluster level, with a minimum cluster size of 100 contiguous voxels.
CAP = standardized age-CAG product (Ross et al., 2014); dlPFC = dorsolateral prefrontal area; GMV = gray matter volume; MCC = middle cingulate cortex; MNI = Montreal Neurological Institute; PBA-s = short-Problem Behaviors Assessment (Callaghan et al., 2015); VBM = voxel-based morphometry.

For the exploratory cross-sectional whole-brain VBM results, we found that higher apathy severity was significantly associated with reduced GMV across sub-cortical and cortical territories. Furthermore, the pattern of GMV was found to be similar both with and without controlling for the effects of CAP, a proxy measure of disease state, and non-apathetic neuropsychiatric symptoms. Results are presented when controlling for all aforementioned covariates of no-interest (**Figure 5.3; Table 5.4**).

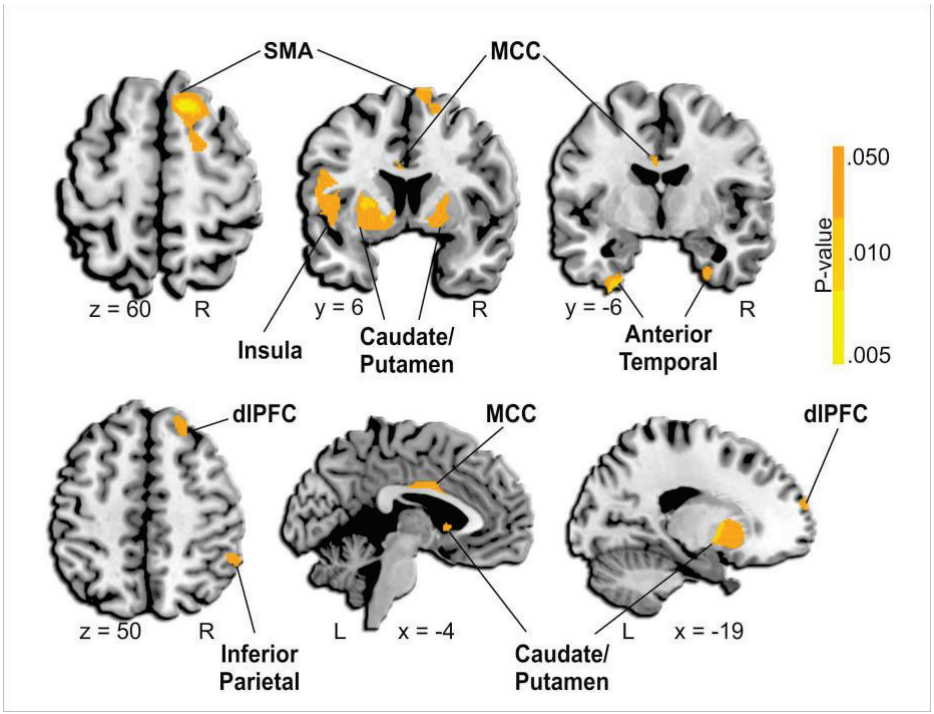


Figure 5.3. Results of cross-sectional voxel-based morphometry analysis with structural T1-weighted images. Slices display regions where lower gray matter volume is associated with higher apathy levels. For illustrative purposes, results are shown at three discrete significance levels (uncorrected) applied at voxel-level, with a minimum cluster size of 100 contiguous voxels: $P < 0.05$, $P < 0.01$, $P < 0.005$. Slice position is labeled in Montreal Neurological Institute coordinates. dlPFC = dorsolateral prefrontal area; L = left; MCC = middle cingulate cortex; R = right; SMA = supplementary motor area.

Table 5.4. Cross-sectional VBM analysis of GMV and PBA-s apathy

Anatomical region	Cluster size	T value	*P* value	MNI Coordinates (*x, y, z*)
R SMA	1239	4.04	< 0.001	15 23 65
L Inferior temporal lobe	346	3.17	0.002	-29 -9 -45
L Pallidum/putamen/caudate head	1958	2.94	0.003	-20 2 2
L Insula (BA 13)	965	2.85	0.004	-45 5 11
R Pallidum/putamen/caudate head	696	2.78	0.004	20 2 -3
L dlPFC (BA 10)	107	2.50	0.008	-21 63 23
R Inferior parietal	121	2.45	0.010	57 -48 50
R Inferior temporal lobe	215	2.42	0.013	24 -15 -38
R dlPFC (BA 10)	112	2.15	0.019	38 35 23
L MCC (BA 24)	122	2.04	0.024	-6 -2 32

P values were significant at a threshold of $P < 0.05$ applied at voxel-level, with a minimum cluster size of 100 contiguous voxels. BA = Brodmann area; CAP = standardized age-CAG product (Ross et al., 2014); dlPFC = dorsolateral prefrontal area; GMV = gray matter volume; MCC = middle cingulate cortex; MNI = Montreal Neurological Institute; PBA-s = short-Problem Behaviors Assessment (Callaghan et al., 2015); SMA = supplementary motor area; VBM = voxel-based morphometry.

5.3.3 Generalized Linear Mixed-Effects Models

When examining the likelihood ratio test between the two apathy models, it was found that Model 1.1 (that with an interaction term between baseline MCC and time) was of superior likelihood, demonstrating a statistically significant better fit than the null Model 1.0 ($\chi^2(2) = 6.5$, $P = 0.040$). This finding was further exemplified through the superior Akaike's information criteria weight for Model 1.1 ($W = 0.773$) when compared to the null ($W = 0.227$).

When evaluating the significance of individual variables (**Table 5.5**), the interaction term of Model 1.1 illustrates that a small MCC volume is capable of predicting how apathy levels change longitudinally. Specifically, the negative β Estimate value indicates that, as apathy increases over time, those with larger initial MCC volumes experience a slower rate of change in apathy, demonstrating a plateau or even a slight decrease in apathy. On the other hand, those with a smaller initial MCC volume increased in apathy, and at a faster rate (**Figure 5.4**).

Table 5.5. Apathy and cognitive decline as predicted by right MCC volume *(continued on next pages)*

	***β* Estimate**	***SE***	***Z* value**	***P* value**
Model 1.0 – PBA-s apathy null AIC = 738.1; *W* = 0.227				
CAP	0.199	0.115	1.724	n.s.
Neuropsychiatric disturbances[a]	0.223	0.063	3.573	< 0.001
Time[b]	–0.010	0.076	-0.130	n.s.
Model 1.1 – PBA-s apathy AIC = 735.7; *W* = 0.773				
Right MCC volume	-0.183	0.134	-1.363	n.s.
CAP	0.128	0.119	1.073	n.s.
Neuropsychiatric disturbances[a]	0.218	0.060	3.649	< 0.001
Time[b]	-0.047	0.068	-0.690	n.s.
Right MCC volume × Time	-0.184	0.075	-2.473	0.013
Model 2.0 – PBA-s depression null AIC = 835.4; *W* = 0.702				
CAP	-0.110	0.191	-0.574	n.s.
Neuropsychiatric disturbances[a]	0.623	0.087	7.116	<0.001
Time[b]	0.277	0.218	1.270	n.s.
Model 2.1 – PBA-s depression AIC = 837.1; *W* = 0.298				
Right MCC volume	-0.383	0.254	-1.506	n.s.
CAP	-0.221	0.215	-1.029	n.s.
Neuropsychiatric disturbances[a]	0.618	0.088	7.060	<0.001
Time[b]	0.306	0.220	1.392	n.s.
Right MCC volume × Time	-0.230	0.215	-1.071	n.s.
Model 3.0 – UHDRS-cogscore null AIC = 1778.2; *W* = 0.061				
CAP	-0.273	0.055	-4.950	<0.001

Neuropsychiatric disturbances[a]	-0.026	0.011	-2.321	0.020
Time[b]	-0.029	0.021	-1.393	n.s.
Model 3.1 – UHDRS-cogscore AIC = 1772.7; *W* = 0.939				
Right MCC volume	0.124	0.058	2.133	0.033
CAP	-0.225	0.059	-3.836	<0.001
Neuropsychiatric disturbances[a]	-0.025	0.011	-2.291	0.022
Time[b]	-0.046	0.020	-2.274	0.023
Right MCC volume × Time	0.046	0.018	2.521	0.012

All regression estimates are standardized. *P*-values significant at $P<0.05$.

[a] Neuropsychiatric disturbances evaluated through the PBA-s, calculated by subtracting the apathy sub-score from the total score in Model 1, the depression sub-score from the total score in Model 2, and utilizing the total PBA-s score (without subtractions) in Model 3.

[b] Time in days (accumulative, time at first assessment is zero).

AIC = Akaike's information criteria; CAP = standardized CAG-age product (Ross et al., 2014); MCC = middle cingulate cortex; *SE* = standard error; PBA-s = short-Problem Behaviors Assessment (Callaghan et al., 2015); UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score (Huntington Study Group, 1996); *W* = Akaike's information criteria weight (Burnham & Anderson, 2002; Long, 2011).

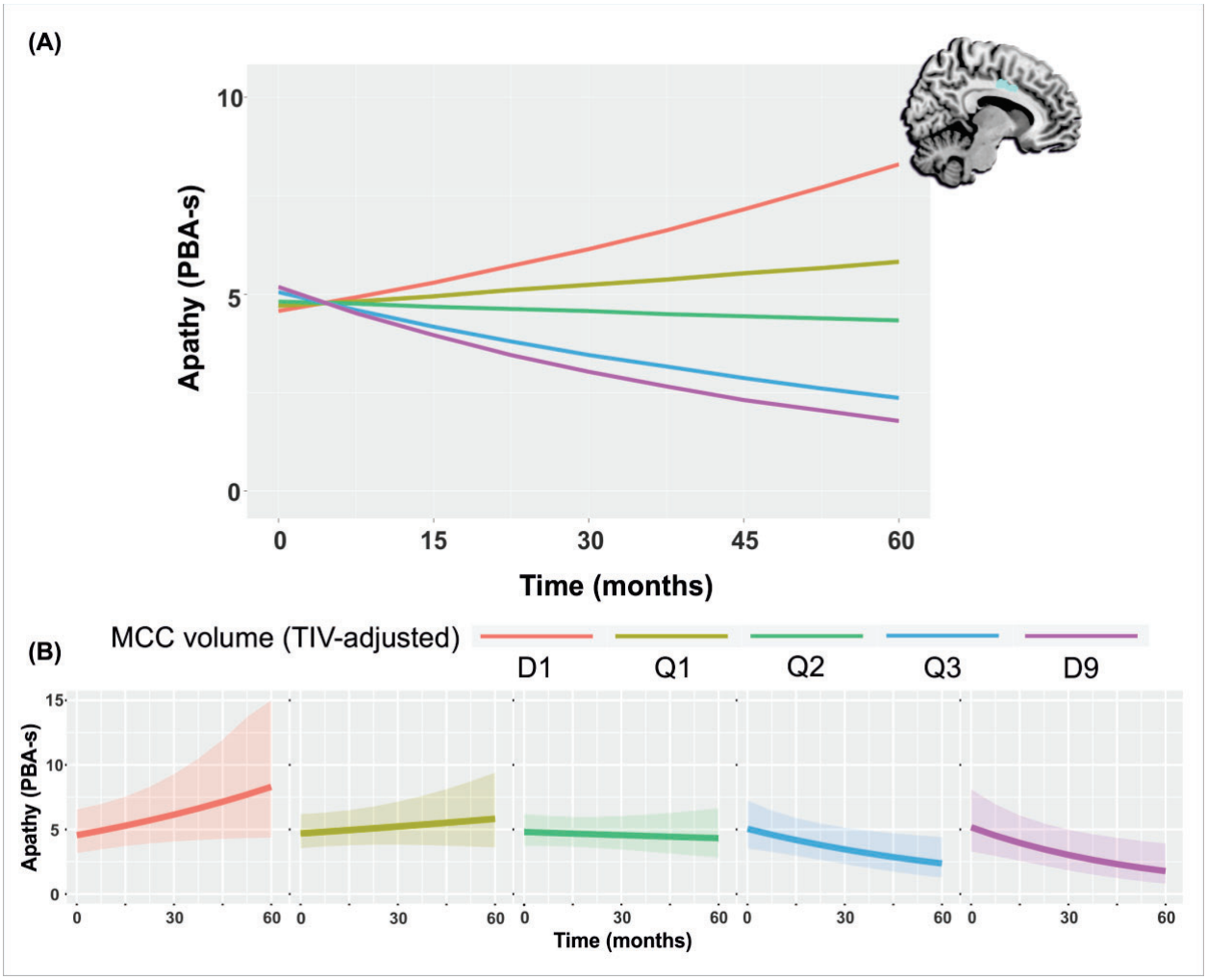


Figure 5.4. Smaller initial MCC volume predicts a faster rate of apathy development across time, demonstrated through Model 1.1 **(A)**, with split-view regression lines of model predictions at 95% confidence interval **(B)**. D1 = first decile; D9 = ninth decile; MCC = middle cingulate cortex; PBA-s = short-Problem Behaviors Assessment; Q1 = first quartile; Q2 = median; Q3 = third quartile; TIV = total intracranial volume.

In follow-up models of PBA-s depression and UHDRS-cogscore, the inclusion of the interaction between initial MCC volume and time resulted in a statistically superior model predictive of executive dysfunction (Model 3; $\chi^2(2) = 9.45$, $P = 0.009$), but not depression (Model 2; $\chi^2(2) = 2.29$, $P = 0.318$), compared to their respective null models (**Table 5.5**). Lastly, longitudinal UHDRS-cogscore, but not depression, was significantly associated with apathy development (**Table 5.6**).

Table 5.6. Apathy as predicted by cognitive decline

	β Estimate	*SE*	*Z* value	*P* value
PBA-s apathy AIC = 830.1; *W* < 0.001				
PBA-s depression	-0.021	0.049	-0.435	n.s.
PBA-s apathy AIC = 665.8; *W* > 0.999				
UHDRS-cogscore	-0.284	0.100	-2.844	0.004

All regression estimates are standardized. *P*-values significant at $P < 0.05$.
AIC = Akaike's information criteria; *SE* = standard error; PBA-s = short-Problem Behaviors Assessment (Callaghan et al., 2015); UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score (Huntington Study Group, 1996); *W* = Akaike's information criteria weight (Burnham & Anderson, 2002; Long, 2011).

5.4 Interpretation

The goal of the present study was to investigate the longitudinal development of apathy, compared with depressive and executive functional outcomes, as predicted by atrophy and initial vulnerability in regional GMV. Utilizing VBM, we revealed that specific GMV atrophy in the right MCC (BA 24) was related to increases in apathy severity over time, but not depression or executive dysfunction. Furthermore, vulnerability in the MCC volume at baseline successfully predicted the longitudinal severity and progression of apathy, even after controlling for CAP, a proxy of disease state, as elucidated through the generalized linear mixed-effects models. In brief, the interaction term in Model 1.1 highlights that initial vulnerability (smaller volume) in the MCC may be predictive of those individuals who were more likely to develop apathy or experience worsening apathy at a future point in time. By extension, initial MCC volume additionally informed a prognosis of worsening executive functional outcomes.

Previously known as the dACC (Vogt, 2016), the MCC has long been implicated in goal-directed behaviors (i.e., those that are disrupted in apathy), thus serving as a neurological interface between motivation and action execution, especially for effortful actions (Allman et al., 2006; Mega et al., 1997; Theleritis et al., 2014). Indeed, damage to this region has been confirmed to play a role in the manifestation of apathy (Kos et al., 2016; Le Heron, Apps., et al., 2018) and abulia (Lavretsky et al., 2008) across a range of clinical neurological disorders. Moreover, previous studies postulate that the MCC may form a

part of a medial frontostriatal apathy circuit innervating the ventral striatum and extending to the OFC (Bonelli & Cummings, 2007; Guimarães et al., 2008; R. Levy & Dubois, 2006; Mega et al., 1997; P. H. Robert et al., 2010). Damage to this MCC circuit at either the subcortical or cortical level may therefore directly contribute to the development of emotional, cognitive, and behavioral inactivity and a loss of spontaneity (Allman et al., 2006) as well as impaired decision-making (Theleritis et al., 2014).

Examining the frontostriatal circuits implicated in apathy sheds light on the characteristic complex of both cortical and subcortical territories involved in apathy in HD. In the present study, atrophy in such subcortical regions was not significantly associated with increased apathy over time. This may be due to the distinct rates of atrophy in the basal ganglia compared with cortical regions in HD, the latter of which may more closely parallel the rate of change in apathy. Indeed, examining GMV cross-sectionally corroborated an association between apathy and both subcortical and cortical territories (see **Figure 5.3; Table 5.4**), wherein lower GMV was associated with higher apathy severity. This pattern of limbic and cognitive regions closely mirrored those found in past literature (Martinez-Horta et al., 2018). Specifically, across both structural and functional modalities, neural correlates have been shown to include the medial OFC, SMA, cingulate, caudate, and ventral striatum, or connectivity between such regions (De Paepe et al., 2019; Delmaire et al., 2013; Martinez-Horta et al., 2018; McColgan et al., 2017), with a disputed involvement of the thalamus (Baake, Coppen, et al., 2018; Misiura et al., 2019). This complex interplay may be due to the multidimensional, transdiagnostic nature of apathy as composed of apathy subdomains, each represented by a discrete underlying neurobiological framework (De Paepe et al., 2019; R. Levy & Dubois, 2006; Pagonabarraga et al., 2015).

All in all, the MCC (BA 24) has been associated with apathy severity in both healthy and neurologically impaired populations (Kos et al., 2016; R. Levy & Dubois, 2006; Moretti & Signori, 2016). For example, apathy in otherwise healthy individuals has been related with decreased salience-related processing in ACC (Onoda & Yamaguchi, 2015) as well as a greater recruitment of ACC and SMA, two neural systems involved in action anticipation (Bonnelle et al., 2016). One case study reported aberrant functional connectivity in the dorsal ACC in patients with abulia compared to controls, even in the absence of structural

damage (Siegel et al., 2014). When examining cross-sectional GM atrophy specifically, reduced GM density or volume in the middle cingulate gyrus has been linked to more severe apathy in frontotemporal dementia (Massimo et al., 2009), Parkinson's disease (Reijnders et al., 2010), and Alzheimer's disease (Apostolova et al., 2007; Bruen et al., 2008) in addition to HD (Martinez-Horta et al., 2018), bilaterally or predominantly in the right hemisphere.

The MCC (BA 24) bears distinct structural and functional connectivity from the more rostral/ventral ACC (Stevens, 2011; Vogt, 2016). In short, while ACC connectivity extends to regions involved in emotion, autonomic function, and reward processing, the MCC shares extensive connections specifically with cognitive- and motor-related cortical regions, including dorsal prefrontal and premotor cortices (Beckmann et al., 2009). In the current study, the fact that apathy development in HD is specifically represented by atrophy in the MCC, as opposed to the ACC, may explain the differential expression of apathy domains in this patient population (De Paepe et al., 2019). Lastly, it is interesting to note that MCC atrophy was not indicative of changes in depression, a disorder often associated with the more rostral/ventral ACC (Koolschijn et al., 2009).

Functionally, the MCC is activated during cognitive and motor-related tasks. This is exemplified in effort-based response-selection and execution, such as when action selection is directed by reward anticipation and reinforcement (Beckmann et al., 2009; Rushworth et al., 2007). Such effort-based decision-making is compromised in individuals with apathy (Kurniawan et al., 2011; Le Heron, Manohar, et al., 2018). Ultimately, the present results underscore the notion that disruption to the integrative functionality of the MCC may sub-serve not only the prognosis of apathy and executive dysfunction in HD, but also the coevolution of these two devastating clinical features.

In this vein, both HD patients and caregivers describe cognitive and neuropsychiatric symptoms as imposing a greater burden on functional capacity and quality of life than motor dysfunction, with no effective treatment for cognitive decline and apathy currently available (Eddy et al., 2016; Tabrizi et al., 2013). Furthermore, 39.2% of gene-carriers may present cognitive and/or neuropsychiatric disturbances in the absence of motor symptoms (Vinther-Jensen et al., 2014), with neuropsychiatric aspects appearing up to ten years prior to clinical diagnosis by motor onset (Duff et al., 2007; Martinez-Horta et

al., 2016). Specifically, increased apathy severity has long been associated with a deterioration of higher order cognitive functions in both healthy aging and neurologically impaired populations, particularly in tasks involving initiation processes and task switching (Kawagoe et al., 2017; Le Heron, Manohar, et al., 2018; Meyer et al., 2015; Sinha et al., 2013; Varanese et al., 2011; Zgaljardic et al., 2007). More recently, apathy was found to predict rates of cognitive decline in premanifest HD individuals (Andrews et al., 2020). Neurobiologically, both apathy and executive dysfunction are related with lesions in frontal cortico-striatal circuitry (Bonelli & Cummings, 2007; Leh et al., 2010). In light of this, future investigation focusing on the interaction between the MCC, apathy, and executive function would be especially relevant in the elucidation of distinct profiles of HD, where the presentation of motor, cognitive, and neuropsychiatric symptoms is heterogeneous at the individual level (Garcia-Gorro et al., 2019).

The present study is not without limitations. First, it is important to note that the sample is not representative of all HD gene-carriers. In particular, the VBM analysis includes only those participants willing to take part in a longitudinal study. In order to minimize this effect of potentially non-random attrition, all longitudinal and cross-sectional data were incorporated in the generalized linear mixed-effects models. As such, while the models included a maximum total of six apathy assessments, a subset of individuals received only one evaluation. Future studies that have the potential to link longitudinal evaluation of neuropsychiatric signs and neural correlates may be more sensitive to detect patterns of atrophy that predate subtle changes in apathy. Indeed, latent difference score models have demonstrated that recent brain changes may indicate the advent of cognitive decline in a coupled-over-time manner (Grimm et al., 2012; McArdle et al., 2004), exemplifying the value of repeated measures in both neuroimaging and behavioral evaluations when evaluating time-dependency relationships. In parallel, complementing longitudinal volumetric neuroimaging with other structural, morphometric, or functional protocols is also of interest, especially as distinct imaging modalities may be more sensitive to different neural substrates (Cercignani & Bouyagoub, 2018).

In line with this limitation, and as previously denoted, the longitudinal, whole-brain analysis of the present study did not expose other elements of the medial frontostriatal apathy circuit beyond the MCC (i.e., OFC, ventral striatum). As such, while these findings

elucidate the vulnerability of the MCC as a specific predictor of apathy development over time, this study by no means simplifies the picture of apathy in HD; rather, it serves to highlight the existing gaps in the study of this multidimensional, transdiagnostic symptom and syndrome. In future studies, the evaluation of apathy subdomains may prove to be more sensitive to disentangling the swath of neural correlates that represent apathy. Such work would be valuable in assessing whether the MCC and other regions are implicated in both neurologically impaired and otherwise healthy individuals in which apathy is prevalent.

Additionally, while not the focus of the study, it should be noted that the UHDRS-cogscore is a limited estimate of cognition, specific to processing speed and executive function (Toh et al., 2014). Furthermore, all UHDRS components are sensitive to age-related decline. For this reason, corrections for CAP were included in all analyses as control covariates.

Lastly, it is important to note that the apathy models accounted for zero-inflation. This relates to the 26.7% (12/45) of individuals that did not develop even mild, sub-clinical signs of apathy over the course of the study. This absence of apathy may be explained by other life factors that protect these individuals from developing apathy, irrespective of their initial MCC size.

This paper provides a whole-brain longitudinal evaluation of the relationship between changes in apathy and atrophy of underlying brain correlates in HD, as such filling a noted gap in the literature. Not only do these findings reveal that a reduction in the MCC volume is significantly related to an increase in apathy severity in HD at the individual level; we also highlighted that initial vulnerabilities in the MCC may be predictive of those individuals who are predisposed to develop apathy and accompanying executive dysfunction at a faster rate in time. As such, this study opens a door to the incipient detection of those individuals who may be prone to develop a more apathetic neuropsychiatric profile in the future. In this case, the personalized management of apathy during an earlier, optimal window may be initiated, including both pharmacological and behavioral interventions. Ultimately, this study may serve as a model for the anticipative evaluation of common neuropsychiatric features in HD, with potential applications to other neurodegenerative diseases as well as otherwise healthy populations suffering from apathy.

5.5 Supplemental Information

Analysis Code in R

```
library(xlsx)
library(glmmTMB)
library(qpcR)
library(performance)

setwd('~/Downloads')
df <- read.xlsx('Mixed_models_data_131020_all.xlsx', sheetIndex=3)

df$ID <- as.integer(1:nrow(df))

lf <- reshape(df, idvar='Code', varying=7:(ncol(df)-1), sep="_", direction='long')
lf <- lf[,c('ID','days','CAP','PBArest','Apathy','nACC_1')]
lf <- lf[order(lf$ID),]

lf$days <- as.numeric(scale(lf$days))
lf$CAP <- as.numeric(scale(lf$CAP))
lf$PBArest <- as.numeric(scale(lf$PBArest))
lf$nACC_1 <- as.numeric(scale(lf$nACC_1))

fit0 <- glmmTMB(Apathy ~ days + CAP + PBArest + (1+days||ID), zi=~1, family=poisson,
data=lf,control=glmmTMBControl(optCtrl=list(iter.max=1e3, eval.max=1e3), profile=T))

fit1 <- glmmTMB(Apathy ~ nACC_1 * days + CAP + PBArest + (1+days||ID), zi=~1,
family=poisson, data=lf, control=glmmTMBControl(optCtrl=list(iter.max=1e3,
eval.max=1e3), profile=T))

results0 <- summary(fit0)
results1 <- summary(fit1)

anova(fit0,fit1)

x <- c(results0$AICtab[[1]], results1$AICtab[[1]])
akaike.weights(x)

check_collinearity(fit0, component = "conditional")
check_collinearity(fit1, component = "conditional")
```

Chapter 6
Results: Study 3

This study corresponds to:

De Paepe, A. E., Garcia-Gorro, C., Martinez-Horta, S., Perez, J. P., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Santacruz, P., Muñoz, E., Mareca, C., Ruiz-Idiago, J., de Diego-Balaguer, R., & Camara, E. (2022). Delineating apathy profiles in Huntington's disease with the short-Lille Apathy Rating Scale. *Parkinsonism & Related Disorders*, 105, 83–89. https://doi.org/10.1016/j.parkreldis.2022.10.025

Chapter 6 | Results: Study 3

Delineating apathy profiles in Huntington's disease with the short-Lille Apathy Rating Scale

Apathy, a prevalent feature in neurological disorders including HD, is characterized by a reduction in goal-directed behavior across cognitive, auto-activation (i.e., self-activating thoughts/behavior), and emotional domains, as described in *§ Chapter 1 | Introduction*. Nonetheless, current diagnostic criteria are incapable of distinguishing multidimensional apathy profiles. Meanwhile, the LARS-s bears potential as an operative diagnostic tool to disentangle apathy dimensions in clinical practice. The present study thereby examines the psychometric properties and factor structure of the LARS-s to tap into apathy profiles and their underlying neural correlates in HD. Forty HD individuals were scanned and evaluated for apathy using the LARS-s, assessed for reliability and validity in HD, and the PBA-s. To study the dimensional structure of apathy, principal component analysis of the LARS-s was implemented. Resulting factors were associated with GMV through whole-brain VBM. In summary, the LARS-s demonstrated satisfactory psychometric properties, sharing convergent validity with PBA-s apathy and discriminant validity against depression. Principal component analysis resulted in three factors representative of apathy profiles across cognitive, auto-activation, and emotional domains. Anatomically, global apathy was significantly related with large-scale motor, cognitive, and limbic networks. Exploratory analyses of apathy profiles revealed correspondence between each factor and distinct cortical and subcortical nodes. In conclusion, the LARS-s is capable of capturing the multidimensional spectrum of apathy. At the same time, apathy profiles in HD are underpinned by functionally diverse neural networks. Such findings promote the continued study of apathy domains to pinpoint personalized therapeutic targets in neurologic disorders in addition to HD.

6.1 Background

Apathy, a quantitative reduction in goal-directed behavior not attributable to reduced consciousness (R. Levy & Dubois, 2006) is a debilitating condition that affects day-to-day functioning and social life. Recognized as an independent syndrome from depression, apathy is a frequent pathological condition in many neurological disorders. However, no effective pharmacological or psychosocial treatment is presently available.

Classically, apathy is composed of three subdomains: cognitive, auto-activation deficit, and emotional (R. Levy & Dubois, 2006), although distress and social subtypes have also been proposed (Ang et al., 2017). Cognitive apathy is attributed to reduced executive functioning required to develop a plan, while emotional apathy is characterized by blunted affect. Meanwhile, auto-activation deficit, posited as the most severe apathy domain, translates to a decrease in self-activating thoughts or behavior (e.g., "I need a push to get started on things"). In recent years, the LARS-s has been validated as a clinical tool to evaluate distinct domains of apathy in patients with Parkinson's disease (Dujardin et al., 2013). The LARS-s is a standardized patient-based interview that takes advantage of a structured dichotomous scale, thereby reducing subjective interpretations. Its widespread implementation has been recommended by the Movement Disorder Society Task Force. As such, this scale lends a clearer view of the multidimensional facets of apathy, with applications in patient follow-up and treatment efficacy assessment.

However, apathy is still diagnosed as a one-dimensional entity (i.e., global apathy) in clinical practice. This may be due to the lack of consensus regarding the classification and operationalization of apathy subdomains. Therefore, the brain correlates of apathy are mainly understood through a nonspecific framework.

Across studies, global apathy has been attributed to disruptions in large-scale networks that span frontostriatal and inferior-parietal territories (R. Levy & Dubois, 2006; Quang et al., 2021). In such a way, neuroimaging has elucidated relationships between apathy and critical structural nodes within functionally diverse circuits. However, there is a gap in the understanding of neurobiological correlates of specific apathy domains.

Nonetheless, recent research has begun to tap into the structural underpinnings of apathy sub-architecture. For example, in both Alzheimer's disease and behavioral-variant frontotemporal dementia, reduced GMV in both cortical and subcortical regions has been differentially linked with cognitive, initiation, and reward-based apathy subdomains (Fernandez-Matarrubia et al., 2018; Kumfor et al., 2018; Wei et al., 2019). These studies further illuminated disparities in the frequency and severity of emotional and executive subdomains according to patient population (Fernandez-Matarrubia et al., 2018; Kumfor et al., 2018; Wei et al., 2019). Similarly, specific apathy domains were differentially expressed in subtypes of primary progressive aphasia, with the semantic-variant subtype exhibiting highest levels of executive and initiation apathy (Quang et al., 2021). These findings underscore that dysfunctions in distinct frontostriatal circuits may sub-serve each apathy dimension, whose interaction may give rise to disease-specific apathy profiles. At the same time, such studies highlight similarities in the underlying network even across neurologic conditions.

In HD, apathy is considered a characteristic feature, exhibiting longitudinal progression even in premanifest individuals and serving as a predictor of functional decline (Ross et al., 2014). However, neurobiological mechanisms of apathy in HD are understudied and replete with discrepancies. Moreover, no scale has yet been validated for the evaluation of apathy in HD, instead measured using the lack of initiative component of the PBA-s. This semi-structured interview is limited in that it records each neuropsychiatric feature as a uniform construct (frequency × severity), precluding the detection of nuanced but clinically meaningful disturbances in apathy, especially if the rater is unfamiliar with its multidimensional manifestations. Conversely, the LARS-s exhibits potential to capture inter-individual variability in the presence and degree of apathy profiles, urging its validation in neurologic conditions other than Parkinson's disease.

Recent work has revealed that executive and initiation components of apathy are clinically relevant in HD (Atkins et al., 2021). Yet, to date, only one study has evaluated the anatomy of such apathy subdomains in HD (De Paepe et al., 2019). Employing the LARS-s, the authors found dysfunctions in specific WM tracts were associated with auto-activation deficit and cognitive apathy. Accordingly, it is expected that the GM nodes connected by such tracts may also reflect variability in apathy profiles, although these

relationships have yet to be investigated. Furthermore, no quantitative assessment of LARS-s domains has yet been carried out.

In this vein, the goal of the present study is two-fold: (1) assess the reliability, validity, and dimensionality of the LARS-s in HD; (2) explore potential GM correlates of apathy profiles. Overall, by merging a multidimensional evaluation of apathy with neuroimaging analysis at the whole-brain level, the present study strives to highlight anatomical correlates of apathy sub-architecture in HD, serving as a model for the study of apathy profiles in other neurologic disorders.

6.2 Study Design

6.2.1 Participants

Participants' demographics are detailed in **Table 6.1**. While HD is formally diagnosed based on motor onset, neurodegeneration and accompanying neuropsychiatric dysfunction often presents years prior to conversion to motor-manifest (Ross et al., 2014). Because the main focus was apathy, we studied the disease as a continuum, as has been carried out in previous studies (Atkins et al., 2021; Davis et al., 2022; Sampedro et al., 2019). Therefore, while not all participants displayed motor symptoms (**Table 6.1**), each was a genetically confirmed HD gene-carrier (43.65 ± 2.97 CAG repeats). No participants reported previous history of traumatic brain injury or neurological disorder beyond HD.

Table 6.1. Sociodemographic and clinical characteristics of study participants

	Premanifest	Manifest	HD gene-carriers
N	18	22	40
Sex (f/m)	16/2	12/10	28/12
Age (years)	39.33 ± 9.51	52.64 ± 10.30	46.65 ± 11.89
Education (years)	13.78 ± 2.65	10.86 ± 2.90	12.18 ± 3.12
CAG	43.56 ± 2.73	43.73 ± 3.21	43.65 ± 2.97
CAP	83.70 ± 21.71	111.59 ± 18.15	99.04 ± 24.09
UHDRS-TMS	2.41 ± 4.11, *N* = 17	21.55 ± 11.85	13.21 ± 13.31, *N* = 39
UHDRS-cogscore	304.11 ± 60.42	183.45 ± 59.53, *N* = 20	240.61 ± 85.00, *N* = 38
TFC	12.93 ± .27, *N* = 14	11.32 ± 1.99	11.94 ± 1.74, *N* = 36
PBA-s total	9.24 ± 17.56, *N* = 17	18.14 ± 17.97	14.26 ± 18.12, *N* = 39
PBA-s apathy	2.12 ± 4.15, *N* = 17	5.50 ± 5.07	4.03 ± 4.93, *N* = 39
*% clinically relevant**	*41.1%*	*77.3%*	*61.5%*
LARS-s	-7.89 ± 5.12	-6.50 ± 4.76	-7.12 ± 4.91

Data presented as *mean ± standard deviation*. *N* detailed in individual cells where differing. Premanifest and manifest grouped based on Unified Huntington's Disease Rating Scale diagnostic confidence score for motor abnormalities.
* Cut-off defined as a PBA-s apathy score ≥ 2.
CAG = length of cytosine-adenine-guanine base length repeats of the mutated allele; CAP = standardized CAG-age product; f = females; HD = Huntington's Disease; m = males; *N* = number of participants; UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score; UHDRS-TMS = Unified Huntington's Disease Rating Scale total motor score; TFC = Total Functional Capacity; PBA-s = short-Problem Behaviors Assessment.

6.2.2 Clinical Evaluation

Participants were assessed with the UHDRS evaluation (Huntington Study Group, 1996), comprising subscales for motor function, cognition (UHDRS-cogscore), and TFC. The standardized CAP score, computed as CAP = 100 × age × (CAG – 35.5) / 627, served as a measurement of HD state (Ross et al., 2014). Clinical assessments were carried out by neurologists/neuropsychologists specializing in movement disorders. The study was approved by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975. All participants signed written informed consent.

6.2.2.1 Neuropsychiatric symptoms

The LARS-s was employed to study apathy dimensions (Dujardin et al., 2013). This structured interview contains twelve discriminant items from seven domains for apathy detection: daily productivity, interests, taking the initiative, novelty seeking, motivation and voluntary actions, emotional responses, and social life. Example questions include, "What are you interested in?" and "Do you take part spontaneously in daily living activities, or do you need to be asked?" In the present study, global apathy is measured as the total score (range: –15 to +15) of the LARS-s.

Neuropsychiatric symptoms were additionally evaluated using the PBA-s, a semi-structured interview that consists of eleven items: depressed mood, suicidal ideation, anxiety, irritability, anger or aggression, lack of initiative (apathy), preservative thinking/behavior, obsessive-compulsive behavior, paranoid/delusional thinking/behavior, hallucinations, and disorientation. Scores are calculated as frequency × severity (range: 0 to 16) for each symptom. As a control variable, non-apathetic neuropsychiatric disturbances were calculated as the sum of all ten additional (non-apathetic) items, allowing the examination of apathy as an independent neuropsychiatric feature from the others.

6.2.3 MRI Acquisition and Processing

MRI data were acquired with a 3T whole-body MRI scanner (Siemens Magnetom Trio; Hospital Clinic, Barcelona), using a 32-channel phased array head coil to procure structural T1-weighted images (magnetization-prepared rapid-acquisition gradient echo sequence), 208 sagittal slices, repetition time = 1970ms, echo time = 2.34ms, inversion time = 1050ms, flip angle = 9°, field of view = 256mm, 1mm isotropic voxel with no gap between slices.

Cross-sectional morphometric analysis was conducted using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) in SPM12 (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v17.a, Mathworks, Natick, MA).

GM segmentations (unified segmentation algorithm) were used to create a customized DARTEL template. Flow fields were applied to each participant's native GM image. Transformations from customized template to standard space were applied to individual GM segmentations to achieve spatial normalization in MNI space. Resulting GM normalized images were modulated by their Jacobian determinants and spatially smoothed (FWHM = 8mm).

TIV was calculated as the sum of GM, WM, and cerebrospinal fluid for each participant. An explicit absolute masking with a threshold of 0.2 was applied in model selection (i.e., including only those voxels with > 20% probability of being GM) to more selectively distinguish GM boundaries from WM.

6.2.4 Data Analysis

Statistical analysis of group demographics, factor analysis, and clinical data was performed in SPSS (v.25, SPSS Inc., Chicago, USA). Multiple regression models for VBM were developed in CAT12.

False discovery rate was used to correct Pearson's correlations for multiple comparisons based on the number of tests (q = 0.05). Both raw P-values (P) and the P-adjusted values (P-adj) are reported in text. Differences were considered statistically significant when P-adj ≤ 0.05.

6.2.4.1 Psychometric Properties and Dimensionality of LARS-s

Test reliability was assessed through Cronbach's standardized α and average inter-item correlation. We next implemented principal component analysis on the domain scores of the LARS-s to characterize the underlying factor structure of apathy across participants. Principal component analysis was conducted with Varimax rotation and a list-wise deletion of missing cases (N = 40), with the seven LARS-s variables for inclusion. Extraction communality values illustrate the estimated variance of each item accounted for by extracted factors.

In order to assess convergent validity and discriminant validity against depression, Poisson regression analyses between LARS-s apathy and PBA-s apathy or depression scores, respectively, was performed. Lastly, Pearson's correlations were conducted between apathy with CAP and TFC to explore the relationship between apathy and clinical markers of disease progression.

6.2.4.2 VBM of Structural T1-Weighted Images

Smoothed GM images were entered into voxel-wise multiple regression to examine the effect of GMV on apathy. TIV, age, education, sex, and CAP were entered into the model as covariates of no interest to control for potential direct or indirect effects on LARS-s global or subdomain scores. Non-apathetic neuropsychiatric disturbances were included as an additional covariate of no interest when analyzing global apathy with the LARS-s.

For global apathy, significant results were identified at $P < 0.005$ and corrected for multiple comparisons at cluster-level ($P < 0.05$), with a minimum cluster size = 25 contiguous voxels. When examining apathy profiles, an exploratory threshold was applied ($P < 0.005$ at voxel-level, uncorrected). Anatomic and cytoarchitectonic areas were identified using the Automated Anatomical Labeling Atlas included in the xjView toolbox (http://www.alivelearn.net/xjview).

6.3 Results

The primary goals of the present study are, on the one hand, to examine the psychometric properties and factor structure of the LARS-s in HD and, on the other, to explore potential GM correlates of apathy profiles in HD as a neurodegenerative disease model.

6.3.1 Psychometric Properties and Dimensionality of LARS-s

Internal consistency between the twelve discriminant items was determined as a Cronbach's standardized $\alpha = 0.661$, demonstrating satisfactory internal consistency, and an average inter-item correlation of $r = 0.140$. The two novelty-seeking items demonstrated the lowest corrected item-total correlation when averaged across the domain.

The data satisfied conventional requirements for factor analysis (Kaiser-Meyer-Olkin measure of sampling adequacy = 0.543; Bartlett's test of sphericity $P < 0.001$). In accordance with the three-dimensional model of apathy, principal component analysis extracted three factors with Eigenvalues > 1, collectively explaining 69.2% of total variance (**Table 6.2; Figure 6.1A**). The social life component demonstrated a low extraction communality value = 0.446, whereas all other components exemplified extracted communality values > 0.65. In addition to its primary loading on Factor II, the initiative component presented a relatively strong loading on Factor I (0.534).

Table 6.2. Principal component analysis of LARS-s items, rotated component matrix

Item*	EC	Component loadings		
		Factor I: Cognitive	Factor II: Auto-activation	Factor III Emotional
Daily productivity	0.661	**0.805**	0.062	0.097
Interests	0.679	**0.801**	-0.032	0.192
Initiative	0.753	0.534	**0.675**	-0.113
Novelty seeking	0.788	-0.214	0.413	**0.757**
Motivation	0.791	0.033	**0.885**	0.083
Emotional responses	0.723	0.282	-0.217	**0.772**
Social life†	0.446	0.610	0.213	-0.168
% Variance	-	32.9%	18.8%	17.5%

Factor loadings > 0.65 are highlighted in **bold**.
† The social life component was not extracted due to low communality value.
EC = extraction communality values; LARS-s = short-Lille Apathy Rating Scale.

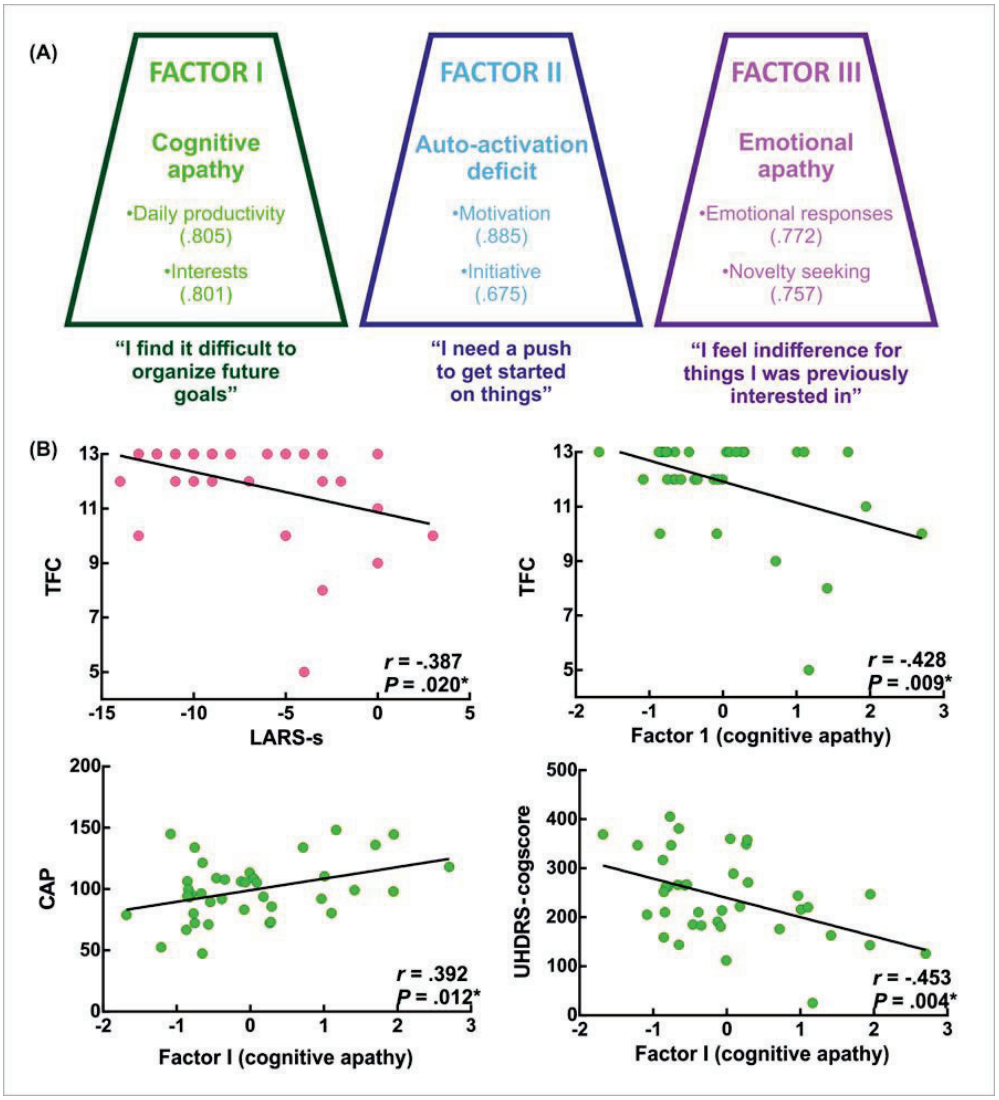


Figure 6.1. Principal component analysis of LARS-s produces clinically meaningful apathy profiles. Derived apathy factors encompassed domains along cognitive, auto-activation deficit, and emotional profiles **(A)**. Apathy was significantly associated with clinical markers of disease progression **(B)**. CAP = standardized CAG-Age Product; LARS-s = short-Lille Apathy Rating Scale; TFC = Total Functional Capacity; UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score.

Given the low principal component analysis extraction communality observed for the social dimension, regression analyses between the LARS-s and PBA-s apathy were performed with and without the LARS-s social domain score (Model 1 and Model 2, respectively). As such, two sets of non-nested models were carried out, the first to assess convergent validity (with PBA-s apathy), and the second for discriminant validity (with PBA-s depression). For apathy, Model 2 (BIC = 301.493) showed better performance in predicting PBA-s apathy scores than Model 1 (BIC = 307.644). Furthermore, Model 2 demonstrated a positive and significant relationship between LARS-s (no social) and PBA-s apathy (β = 0.09, 95% CI[0.05,0.12], P < 0.001), with substantial explanatory power (Nagelkerke's R^2 = 0.48). Meanwhile, PBA-s depression did not correlate with either LARS-s model.

6.3.2 Clinical Disease Progression Markers

Both global apathy and the cognitive apathy profile were significantly related with proxy measures of disease progression (**Figure 6.1B**), with a medium effect size. In particular, global apathy was significantly associated with TFC (r = -0.387, P = 0.020, P-adj = 0.040, N = 40), but not CAP. Meanwhile, cognitive apathy demonstrated a significant relationship with TFC (r = -0.428, P = 0.009, P-adj = 0.036, N = 36) and CAP (r = 0.392, P = 0.012, P-adj = 0.048, N = 40). As hypothesized, only cognitive apathy shared a positive association with UHDRS-cogscore (r = -0.453, P = 0.004, P-adj = 0.016, N = 38). No other apathy factors demonstrated a relationship with CAP, TFC, or UHDRS-cogscore. P-values were adjusted for four comparisons (four apathy scales × one clinical measure).

6.3.3 VBM Results

Utilizing a whole-brain approach, we found that higher apathy scores were sub-served by large-scale networks across cognitive, motor, and limbic territories. Specifically, global apathy was significantly related with reduced GMV in the left middle temporal gyrus (*cluster size* = 761, T = 4.75, P = 0.043, MNI [x = -47, y = -56, z = 20]), right ACC extending to the dlPFC bilaterally (*cluster size* = 1226, T = 4.75, P = 0.013, MNI [x = 8, y = 38, z = 27]), and left superior temporal pole extending to the insula (*cluster size* = 785, T = 4.07, P = 0.040, MNI [x = -53, y = 6, z = 6]) (**Figure 6.2**). When additionally controlling for non-

apathetic neuropsychiatric disturbances as a covariate of no interest, regions maintained the effect. Specifically, previously significant associations between apathy and GMV maintained a trend to the effect in the left middle temporal lobe (*cluster size* = 699, T = 4.70, *P* = 0.050, MNI [*x* = -47, *y* = -57, *z* = 23]), the right ACC (*cluster size* = 683, T = 4.54, *P* = 0.052, MNI [*x* = 8, *y* = 38, *z* = 27]), and the left insula extending to the superior temporal pole (*cluster size* = 536, T = 3.87, *P* = 0.081, MNI [*x* = -51, *y* = 6, *z* = 6]).

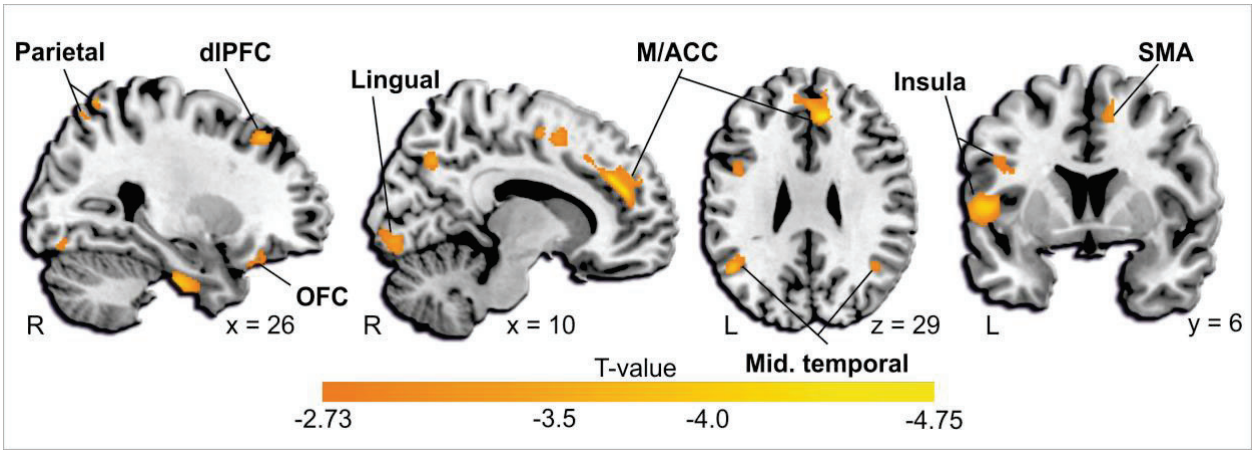


Figure 6.2. Gray matter volume negatively associated with global apathy (short-Lille Apathy Rating Scale). For illustrative purposes, results presented at *P* < 0.005 (uncorrected), *cluster size* = 25. Slice position labeled in Montreal Neurological Institute coordinates. ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; L = left; MCC = middle cingulate cortex; R = right; SMA = supplementary motor area.

Exploratory thresholds revealed further associations between global apathy and frontostriatal and inferior-parietal networks encompassing cortical and subcortical regions (**Figure 6.3A; Table 6.3**).

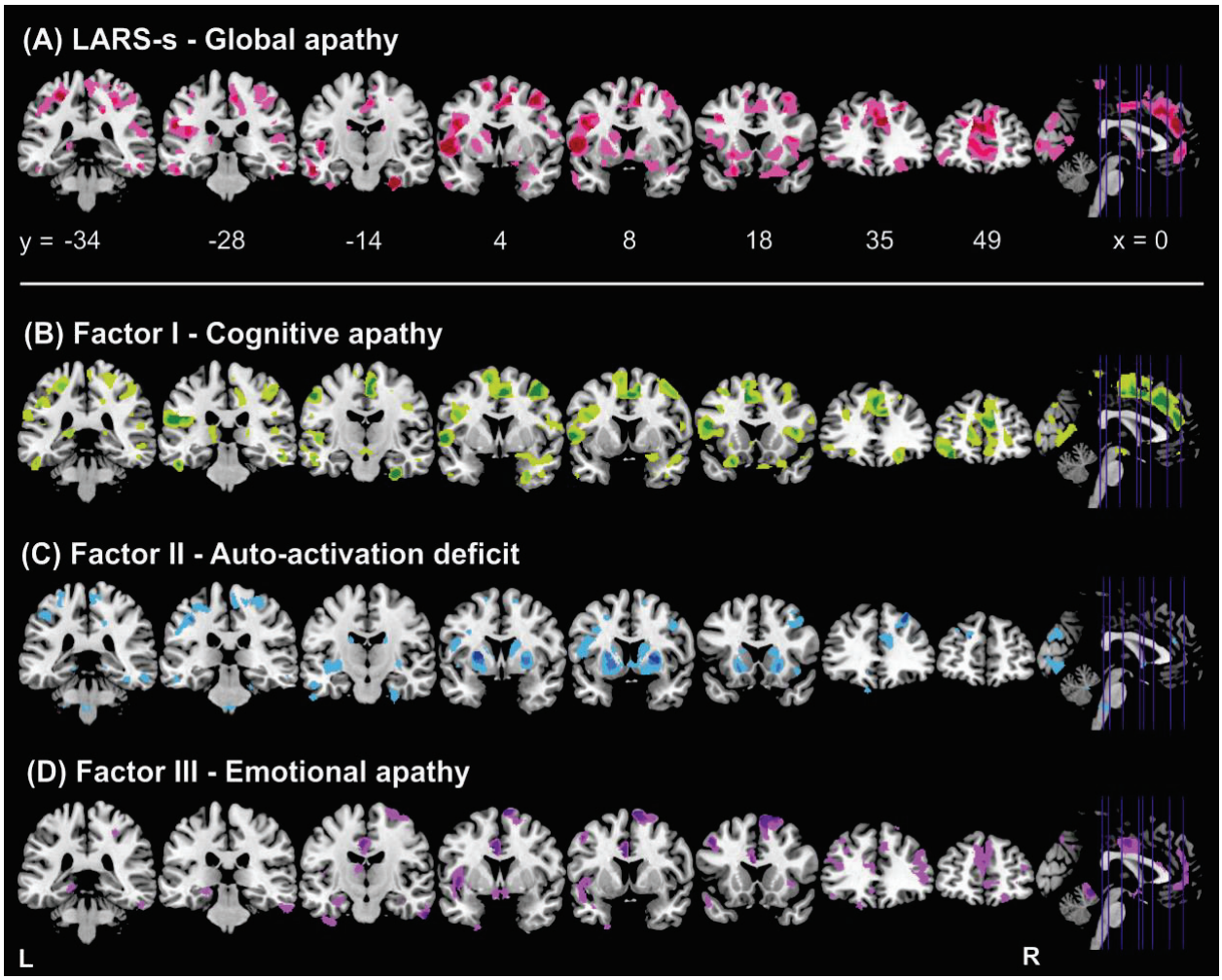


Figure 6.3. Gray matter volume negatively related with apathy profiles, namely **(A)** global, **(B)** cognitive, **(C)** auto-activation, and **(D)** emotional apathy. For illustrative purposes, cluster masks mapped at three thresholds: $P < 0.05$, $P < 0.01$, $P < 0.005$. Slice position labeled in Montreal Neurological Institute coordinates. L = left; LARS-s = short-Lille Apathy Rating Scale; R = right.

Table 6.3. VBM analysis of GMV and global apathy severity (*continued on next page)*

Anatomical region	Hemisphere	Cluster size	T value	*P* value	MNI Coordinates (*x,y,z*)
Global apathy (LARS-s)					
Middle temporal	L	761	4.75	< 0.001*	-47 -56 20
ACC	R	1226	4.75	< 0.001*	8 38 27
dlPFC	R	-	3.09	-	9 50 30
dlPFC	L	-	3.15	-	-11 48 26
Middle temporal	L	72	4.20	< 0.001	-54 -14 -20
Fusiform	R	353	4.09	< 0.001	29 -15 -33
Superior temporal pole	L	785	4.07	< 0.001*	-53 6 6
Insula	L	-	2.76	-	-45 2 -2
Superior parietal	R	56	3.99	< 0.001	26 -62 66
Inferior parietal	L	457	3.89	< 0.001	-39 -41 50

Middle frontal	R	168	3.78	< 0.001	27 30 45
Inferior temporal	R	108	3.75	< 0.001	59 -21 -18
Precuneus	R	184	3.70	< 0.001	15 -62 42
Lingual	R	427	3.61	< 0.001	9 -86 -6
Fusiform	L	153	3.49	0.001	-32 -69 -8
Lingual	L	-	3.02	-	-23 -66 -8
Precentral	R	186	3.48	0.001	36 2 50
Supramarginal	L	84	3.35	0.001	-54 -26 24
Superior parietal	R	82	3.31	0.001	23 -66 56
SMA	R	123	3.31	0.001	12 6 53
SMA	R	40	3.30	0.001	11 -5 54
SMA	L	77	3.22	0.001	-14 0 65
Cuneus	R	32	3.13	0.002	5 -84 33
OFC	R	45	3.06	0.002	26 24 -26
Fusiform	L	69	3.05	0.002	29 -80 -14
Angular	R	39	2.99	0.003	39 -56 29
Heschl	L	33	2.97	0.003	-45 -17 8
Calcarine	L	29	2.96	0.003	-3 -101 9

* Significant at $P < 0.005$, corrected for multiple comparisons at cluster-level ($P < 0.05$), minimum cluster size = 25 contiguous voxels.
ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; GMV = gray matter volume; L = left; LARS-s = short-Lille Apathy Rating Scale; MCC = middle cingulate cortex; OFC = orbitofrontal cortex; R = right; SMA = supplementary motor area ; VBM = voxel-based morphometry.

When considering apathy profiles, relationships were found between each derived factor and distinct networks (**Table 6.4**). First, cognitive apathy was significantly linked to left inferior-parietal lobe and the dorsomedial prefrontal cortex (dmPFC), specifically the right SMA extending to the right MCC (**Figure 6.3B**). Further associations were evinced in the middle temporal lobe and left thalamus. Second, auto-activation deficit was sub-served by cortical and subcortical regions across cognitive and motor territories (**Figure 6.3C**), including the right lingual gyrus, with non-significant associations in the bilateral putamen, right dlPFC, and left middle temporal areas. Third, emotional apathy was linked with ventral and middle frontal areas of limbic functioning, namely the left insula and ventral ACC (**Figure 6.3D**).

Table 6.4. VBM analysis of GMV and apathy severity across profiles *(continued on next page)*

Anatomical region	Hemisphere	Cluster size	T value	*P* value	MNI Coordinates (*x,y,z*)
Factor I (Cognitive apathy)					
Inferior parietal	L	789	5.23	< 0.001*	-41 -42 50
Lingual	L	293	4.27	< 0.001	-30 -71 -6
Inferior temporal	R	118	4.17	< 0.001	56 -23 -18
SMA	R	890	4.13	< 0.001*	12 -6 57
MCC	R	-	3.76	-	3 -12 50
Middle temporal	L	606	4.12	< 0.001†	-45 -54 20
Fusiform	R	274	4.07	< 0.001	32 -18 -33
Supramarginal	L	338	3.96	< 0.001	-54 -27 23
Inferior frontal operculum	L	205	3.85	< 0.001	-45 15 15
Precentral	R	389	3.65	< 0.001	39 0 47
Thalamus	L	45	3.6	0.001	-20 -32 8
Lingual	R	356	3.57	0.001	21 -75 -8
Superior parietal	L	80	3.56	0.001	-23 -68 54
Superior medial frontal	L	383	3.43	0.001	0 45 24
Anterior insula	R	212	3.4	0.001	42 23 6
Middle frontal OFC	L	71	3.35	0.001	-32 50 -18
SMA	L	115	3.34	0.001	-11 -5 71
Temporal pole	L	173	3.3	0.001	-57 3 2
Superior medial frontal	L	544	3.3	0.001	-3 26 42
Postcentral	L	141	3.3	0.001	-53 -17 45
Postcentral	R	33	3.22	0.001	47 -32 56
Inferior temporal	L	42	3.16	0.002	-53 -30 -23
Angular	R	48	3.15	0.002	39 -54 30
Superior medial frontal	R	29	3.06	0.002	11 53 27
Inferior frontal OFC	L	45	3.01	0.002	-24 21 -24
Factor II (Auto-activation deficit)					
Lingual	R	793	3.98	< 0.001*	8 -87 -5
Superior frontal	L	82	3.89	< 0.001	-21 59 26
Superior occipital	L	143	3.56	0.001	-18 -78 39
dlPFC	R	111	3.54	0.001	27 35 45
Middle temporal	L	53	3.17	0.002	-53 -57 11
Putamen, dorsoposterior	L	238	3.1	0.002	-24 -8 9
Putamen	R	138	3.05	0.002	24 14 8
Putamen, anterioventral	L	38	2.94	0.003	-26 12 -6
Factor III (Emotional apathy)					
SMA	R	594	3.96	< 0.001†	8 5 74
Middle frontal	L	181	3.86	< 0.001	-48 12 42
Inferior temporal	R	118	3.8	< 0.001	63 -18 -35
MCC	L	365	3.7	< 0.001	-6 -6 36
Precuneus	L	53	3.5	0.001	-11 -77 57
Superior temporal	L	72	3.21	0.001	-57 -45 18

ACC	L	84	3.18	0.002	-5 27 15
Insula	L	105	3.07	0.002	-44 5 -2

P-values corrected for multiple comparisons at cluster-level ($P < 0.05$), minimum cluster size = 25.
* Significant ($P < 0.005$).
† Tending toward significance ($P < 0.005$).
ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; GMV = gray matter volume; L = left; MCC = middle cingulate cortex; MNI = Montreal Neurological Institute; OFC = orbitofrontal cortex; R = right; SMA = supplementary motor area; VBM = voxel-based morphometry.

6.4 Interpretation

This study strives to describe the psychometric properties and dimensionality of the LARS-s as well as explore the underlying anatomical framework of the elucidated multidimensional apathy profiles. First, the LARS-s evinced adequate psychometric properties in HD, demonstrating convergent validity with the PBA-s. The LARS-s decomposed into three factors aligning with the classical cognitive, auto-activation deficit, and emotional framework. Second, exploratory neuroimaging analyses revealed involvement of distinct large-scale networks, whereby specific apathy profiles related with reduced GMV in nodes across cognitive, motor, and limbic circuits.

The present psychometric results support the use of the LARS-s to reliably measure apathy as a multidimensional construct in HD, presenting discriminant validity against depression. In the past, apathy research in HD has been conducted either with validated, but non-specific scales, or with designated apathy scales not yet validated in HD. The present work thus shifts the focus in the field, proposing an integrated implementation of the LARS-s and PBA-s in HD to facilitate a comprehensive assessment of apathy in the context of other neuropsychiatric features.

Addressing a noted gap in the literature, the present work deciphered a three-dimensional factor structure within the LARS-s utilizing principal component analysis. This triadic structure is similar to that of recent tools devised to document multidimensional apathy (Ang et al., 2017; Massimo et al., 2014; Radakovic & Abrahams, 2014). Comparable to the Dimensional Apathy Scale (Radakovic & Abrahams, 2014), the LARS-s factor structure revealed a coupling between cognitive and initiation (i.e., auto-activation) components. While the initiation domain loaded mainly in auto-activation deficit, a relatively strong initiation loading was also present in cognitive apathy. The link

between cognitive and motor features has previously been observed in HD (Garcia-Gorro et al., 2019). Similarly, in Alzheimer's disease, latent class analysis revealed that the largest class was composed of a combined executive/initiation apathy profile (Radakovic, Starr, et al., 2017). When examining apathy subdomains across dementia, Alzheimer's, and Parkinson's disease, goal-directed cognitive activity was also found to be most common (Mulin et al., 2011). Such results substantiate the relationship between apathy and cognitive impairment (Andrews et al., 2020). This warrants continued dimensional apathy assessment to probe whether specific subdomains (e.g., cognitive apathy and auto-activation deficit) are predictive of dementia development.

Relatively, emotional apathy explained the least variance. This is comparable to the Apathy Motivation Index, in which the emotional sensitivity factor also demonstrated lower item loadings (Ang et al., 2017). It bears mention that the presence of emotional blunting as a facet of apathy is contended. However, the items contained within the emotional apathy factor (emotional response and novelty seeking) have been previously described as a distinguishable emotional apathy profile, being more severe in behavioral-variant frontotemporal dementia than Alzheimer's disease (Fernandez-Matarrubia et al., 2018).

Both global apathy and the cognitive profile positively related with the clinical marker TFC, the latter also with CAP. Aligning these results with previous research of apathy dimensions in HD (Atkins et al., 2021; De Paepe et al., 2019), the cognitive apathy profile appears to most consistently worsen over the disease course. As expected, only cognitive apathy was associated with UHDRS-cogscore. This is similar to findings in amyotrophic lateral sclerosis, in which the cognitive/behavioral initiation component was positively associated with verbal fluency (Radakovic, Stephenson, et al., 2017).

Neurobiologically, exploratory analyses revealed that global apathy and apathy profiles were associated with specific regions of reduced GMV. Global apathy in HD was significantly related with large-scale networks connecting motor, cognitive, and limbic regions, analogous to previous work (Martinez-Horta et al., 2018). Specifically, similar to the present findings, GM atrophy in the cingulate (De Paepe et al., 2021), dlPFC (Zamboni et al., 2008), left insula (Kumfor et al., 2018), and basal ganglia (Martinez-Horta et al., 2018) has been consistently implicated in global apathy in neurodegenerative disease (De

Paepe et al., 2021; Quang et al., 2021; Wei et al., 2019; Zamboni et al., 2008). The ACC, OFC, and dlPFC constitute nodal points of three main frontostriatal loops. These nodes integrate into a larger network involved in decision-making across action-initiation and reward processing contexts (Bechara, 2000; J. D. Cohen et al., 2000). Meanwhile, the inferior-parietal lobe has more recently been deemed to play a role in apathy, exemplifying involvement in movement intention (Quang et al., 2021). In addition, selective brain lesions to the thalamus have been shown to result in apathy, particularly auto-activation deficit (Blundo & Gerace, 2015; R. Levy & Dubois, 2006; Rochat et al., 2013), in support of the present findings.

Next, we identified diverse neural networks that represented distinct domains of apathy. First, cognitive apathy was linked with dmPFC, inferior-parietal regions, and the thalamus. These results are reflected in behavioral-variant frontotemporal dementia, Alzheimer's disease, and primary progressive aphasia (Kumfor et al., 2018; Quang et al., 2021; Wei et al., 2019). The dmPFC has been associated with forward planning, with a potential role in exploration behaviors (Koechlin, 2016). Meanwhile, the emerging role of the inferior-parietal cortex in action control suggests that this region may sub-serve the initiative and daily productivity aspects within this domain. As such, GMV reduction in such nodes may produce cognitive inertia due to an inability to plan and organize goal-directed behaviors, resulting in a loss of ideas and curiosity pertaining to both routine and new events.

Second, auto-activation deficit, which severely affects spontaneous speech, thought and movement, was represented by cognitive- and motor-related cortical and subcortical areas. Already, the basal ganglia has been selectively implicated in the behavioral (i.e., auto-activation deficit) component (Kumfor et al., 2018). In addition, reduced glucose metabolism in the lingual gyrus was found in apathetic Parkinson's patients, also on the right side (Shin et al., 2017).

Third, those with higher emotional apathy displayed reduced GMV in ventral and middle limbic regions. Previously, emotional apathy comparably correlated with lower GMV in the left insula across neurodegenerative disorders (Kumfor et al., 2018), while insular lesions related with reduced reward sensitivity (Rochat et al., 2013). Limbic temporomesial cortex lesions have also been linked to emotional apathy, disrupting the

flow of emotional valence information from the amygdala and nucleus accumbens to the OFC (Blundo & Gerace, 2015). These limbic underpinnings underscore the clinical phenotype of this profile, which may present as a blunting of emotional response and reward valuation, resulting in reduced incentive-related activity.

Of note, specific anatomical territories exemplified a functional delineation between apathy profiles. Remarkably, the cognitive profile was sub-served by reduced GMV in the MCC, a region regulating action selection, cognitive control, and error conflict, while the emotional profile involved the ventral ACC, which moderates affective processing and emotional reward value (De Paepe et al., 2021).

This domain-specific representation of distinct apathy profiles bears implications for the development of personalized therapeutics. Pharmacologically, cholinesterase inhibitors have been proposed for cognitive and motor apathy variants, having been successfully used to treat apathy in Alzheimer's and Parkinson's disease. Meanwhile, dopaminergic agents may be more effective in treating the emotional variant prevalent in behavioral-variant frontotemporal dementia (Fernandez-Matarrubia et al., 2018). When considering psychosocial interventions, those suffering from cognitive or social profiles may benefit from programs that emphasize fewer distractions or community-based music therapy, respectively (Massimo et al., 2014; Wei et al., 2019).

The current study presents certain limitations. To begin, while LARS-s reliability was satisfactory, clinical validity metrics were merely acceptable. All the same, the determined apathy cut-off corroborated past literature (Dujardin et al., 2013). Furthermore, it is important to note that there is no agreed-upon gold-standard apathy scale. Those in existence are prone to subjective rater bias or less severe self-reporting by individuals with anosognosia. Thus, the development of an objective apathy measure that operationalizes discrete apathy subdomains is essential. Methods that take into account locomotor activity and life space are promising for the quantification of auto-activation deficit, while computerized task-based measures (Massimo et al., 2014) and those that distinguish motor from cognitive effort should also be pursued. In terms of neuroimaging, this study was exploratory in nature; larger cohorts are needed to detect anatomical regions underlying subtle differences in apathy profiles.

This study demonstrates that the LARS-s is a valid and reliable scale capable of capturing the multidimensional spectrum of apathy, a prevalent feature of neurological disorders, including HD, in the clinical context. At the same time, the neuroimaging results highlight that apathy profiles are underpinned by functionally diverse neural networks, including nodes pertaining to large-scale cognitive, motor, and limbic circuits. Overall, this work may serve as a model for future multi-centered studies to further elucidate the fundamental substructure of apathy and its neuroanatomical underpinnings, opening a door to the identification of personalized therapeutic targets in neurologic disorders in addition to HD.

Chapter 7
Results: Study 4

This study has been submitted and is currently Under Review.

De Paepe, A. E., Giannoula, A., Garcia-Gorro, C., Rodriguez-Dechicha, N., Vaquer, I., Calopa, M., Sanz, F., Furlong, L. I., de Diego-Balaguer, R., Camara, E. Mapping longitudinal psychiatric signatures in Huntington's disease.

Chapter 7 | Results: Study 4

Mapping longitudinal psychiatric signatures in Huntington's disease

As a review, while HD is characterized by motor onset, psychiatric disturbances may present years prior and impact functioning. However, there is inter-individual variability in psychiatric expression and progression. This study therefore strived to stratify longitudinal psychiatric signatures that may inform HD prognosis, with potential clinical applications. Forty-six HD gene-carriers (21 premanifest, 25 manifest) underwent the PBA-s for depression, irritability, apathy, and dysexecutive behaviors for up to six longitudinal visits. The Disease Trajectories software, a machine-learning approach, was employed to perform unsupervised clustering of psychiatric trajectories. The main clusters of shared trajectories were assessed for group differences. Overall, the Disease Trajectories analysis software identified two main psychiatric patterns comprising premanifest and manifest patients that explained 54% of the sample. These two clusters evinced a dissociation in the development of depression and irritability; the first cluster was defined by increasing irritability with no depression and the second by a rise-and-fall in depression with no irritability. Both clusters showed a longitudinal increase in clinically relevant apathy and dysexecutive behaviors. Ultimately, through the detection of individual-level psychiatric trajectories with machine-learning, this exploratory study reveals that a dissociation of depression and irritability is apparent even in premanifest stages. These findings underscore individual differences in the severity of longitudinal multivariate clinical characteristics for real-world patient stratification, with implications for precision medicine.

7.1 Background

Psychiatric disturbances constitute a significant clinical feature of many neurologic conditions and are noted to severely impact both functioning and quality of life. One such neurologic condition is HD, a hereditary neurodegenerative disease caused by an abnormal CAG repeat expansion in the *HTT* gene. Classified as a movement disorder, the disease gives rise to the characteristic triad of motor, cognitive, and psychiatric dysfunction. Typically, HD is diagnosed in mid-adulthood, with a greater number of CAG repeats linked with earlier symptom onset (Epping et al., 2016). However, there is significant inter-individual heterogeneity in symptom expression and progression over time, even between monozygotic twins (Waldvogel et al., 2012).

Of note, HD is diagnosed based on motor onset, demarcating the transition from the premanifest to manifest stage. As a result, motor symptoms have conventionally been the primary focus of interventional studies (Sellers et al., 2020). Nonetheless, patients and caregivers attest that psychiatric disturbances bear the greatest burden on day-to-day functioning and quality of life, beyond motor impairment (Eddy & Rickards, 2013; Paulsen et al., 2017; Ready et al., 2008; Sellers et al., 2020). Indeed, a recent study evidenced that caregivers of HD patients with more marked psychiatric disorders (including irritability and obsessive-compulsive behaviors in advanced HD and depression in early HD) experienced greater caregiver burden (Youssov et al., 2022). Moreover, such psychiatric features can present up to fifteen years prior to formal disease diagnosis (Martinez-Horta et al., 2016).

Over the course of HD, almost all patients suffer from at least one psychiatric disturbance (Thompson et al., 2012). Of these, apathy, depression, and irritability are the most common (Paoli et al., 2017). While only apathy has been consistently shown to track disease progression, irritability also evinces a relationship with declining functional capacity (Tabrizi et al., 2013; Thompson et al., 2012). Moreover, a greater prevalence of apathy, irritability, and dysexecutive behaviors has been demonstrated even in premanifest individuals compared to healthy controls (Martinez-Horta et al., 2016).

The progression of depression in HD is less consistent (Julien et al., 2007; Thompson et al., 2012; van Duijn et al., 2014). While depression emerges early in the disease in

premanifest and early manifest stages, it does not necessarily track motor and functional decline (Julien et al., 2007; Thompson et al., 2002, 2012; van Duijn et al., 2014). Indeed, longitudinal analysis has identified at least two distinct premanifest profiles with varying levels of depression, even despite similar motor and cognitive trajectories (Kim et al., 2015).

Overall, there remains unexplained variability in both the type and timing of psychiatric evolution in HD, which does not consistently align with the progression of motor and cognitive symptoms (Duff et al., 2007; Epping et al., 2016; Ravina et al., 2008). Moreover, the association or dissociation between different psychiatric features, such as irritability and depression, is contradictory in HD (Simpson et al., 2019) and also in the general population (Fava et al., 2010). For example, while some studies show a link between apathy, irritability, and depression (Bouwens et al., 2015; Fritz et al., 2018; Litvan et al., 1998; Nimmagadda et al., 2011; van Duijn et al., 2014), others fail to establish this relationship (Burns et al., 1990; Kingma et al., 2008; Naarding et al., 2009; van Duijn et al., 2013).

Studies that do assess latent psychiatric signatures within HD often focus on only one psychiatric domain, such as depression or apathy (De Paepe et al., 2021; Kim et al., 2015), or overall behavioral dysfunction in the context of motor and cognitive symptoms (Biglan et al., 2013). Many other studies are cross-sectional in nature (De Paepe et al., 2019; Garcia-Gorro et al., 2019). Therefore, longitudinal multivariate analyses that probe distinct psychiatric trajectories across multiple domains simultaneously may provide a more accurate representation of disease history. Moreover, such longitudinal analysis bears potential in the stratification of individuals that appear clinically homogenous at onset, with implications for tailored prognostic indications, clinical trials, and personalized medicine.

As such, the present exploratory study aims to identify longitudinal multidimensional psychiatric signatures that can shed light on distinctive trajectories of HD progression. To achieve this, we utilize a modified version of the Disease Trajectories unsupervised clustering analysis. Originally described by Giannoula et al. (2018, 2020), this approach has recently been modified to incorporate time-varying numerical clinical and/or imaging biomarkers, amongst other adaptations (Giannoula et al., 2024). In the present proof-of-

concept application, this framework employs the severity of psychiatric signs at different points in time to stratify HD gene-expansion carriers into subgroups based on shared patterns of psychiatric evolution.

7.2 Study Design

7.2.1 Participants

Demographic and clinical characteristics of participants are detailed in **Table 7.1**. Psychiatric features, which may present prior to motor onset and formal diagnosis, were the focus of the study. As such, the disease was studied as a continuum (Martinez-Horta et al., 2016; Thompson et al., 2012), meaning all participants were confirmed HD gene-expansion carriers at baseline (43.91 ± 3.03 CAG repeats). Diagnostic status was defined as premanifest or manifest based on clinical assessment. Four participants who were initially classified as premanifest transitioned to a manifest state over the course of the study and are identified as phenoconverters.

Table 7.1. Sociodemographic and clinical characteristics of study participants (initial value)

	Premanifest	Phenoconverter†	Manifest	HD total
N	17	4	25	46
Sex (f/m)	13 / 4	4 / 0	14 / 11	31 / 15
Age (years)	36.12 ± 9.75	34.00 ± 2.94	49.72 ± 9.83	43.33 ± 11.66
Education (years)	14.06 ± 4.12	12.75 ± 2.99	11.92 ± 4.03	12.78 ± 4.04
CAG	43.71 ± 2.64	44.00 ± 2.83	44.04 ± 3.40	43.91 ± 3.03
CAP	45.16 ± 13.39	45.14 ± 10.65	64.14 ± 18.09	55.47 ± 18.36
UHDRS-TMS	0.35 ± 0.61	5.00 ± 4.24	22.12 ± 13.32	12.59 ± 14.42
UHDRS-cogscore	303.29 ± 54.18	275.50 ± 56.44	184.58 ± 55.06	237.51 ± 78.74, *N* = 45
PBA-s total	19.88 ± 23.26	30.50 ± 35.24	18.64 ± 15.71	20.13 ± 20.44

Data presented as *mean* ± *standard deviation*. Premanifest and manifest grouped based on Unified Huntington's Disease Rating Scale diagnostic confidence score for motor abnormalities at first visit (Huntington Study Group, 1996). †Phenoconverter indicates premanifest individuals that converted to manifest over the course of the study.
CAG = length of cytosine-adenine-guanine base length repeats of the mutated allele; CAP = standardized CAG-age product (Ross et al., 2014); f = females; HD = Huntington's Disease; m = males; *N* = number of participants; PBA-s = short-Problem Behaviors Assessment (Callaghan et al., 2015); UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score (Huntington Study Group, 1996); UHDRS-TMS = Unified Huntington's Disease Rating Scale total motor score.

Participants underwent neuropsychiatric evaluation using the PBA-s over a maximum total of six longitudinal visits, including the baseline assessment. The PBA-s is a semi-structured interview administered in the presence of the main caregiver or other knowledgeable informant. The scale consists of five composite behavioral domains: depression (depressed mood, suicidal ideation, anxiety), irritability (irritability,

angry/aggressive behavior), apathy, dysexecutive behaviors (perseverative thinking/behavior, obsessive compulsive behavior), and psychosis (paranoid/delusional thinking/behavior, hallucinations) (Landwehrmeyer et al., 2016). Each domain is calculated as the product of frequency × severity (range: 0-16 for each symptom). A composite domain score > 2 was considered clinically relevant in line with previously published criteria (Martinez-Horta et al., 2016). Due to a high proportion of zero values (91.58%), the psychosis component was excluded from the analysis.

The four resulting PBA-s domains (depression, irritability, apathy, dysexecutive behaviors) were used as inputs for Disease Trajectories clustering. Additionally, all participants were assessed with the UHDRS motor and cognitive evaluation (Huntington Study Group, 1996), as well as the standardized CAP score (CAP = 100 × age × (CAG – 35.5) / 627), a proxy measure of HD state (Ross et al., 2014). Clinical assessments were conducted by neurologists or neuropsychologists specializing in movement disorders. Medication use (specifically SSRIs, SARIs, NASSAs, NSRIs, NDRIs, benzodiazepines, tetrabenazines, antipsychotics, and anti-epileptics) was also recorded at baseline.

On average, participants completed 4.12 ± 1.54 assessments with a mean inter-assessment duration of 13.96 ± 4.04 months. Thirty-seven participants (80.4%) completed at least three visits, while nine participants completed one or two visits. This resulted in 189 total psychiatric evaluations. No participants reported previous history of neurological disorder other than HD. The study was approved by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975, and all participants provided written informed consent.

7.2.2 Disease Trajectories Clustering Analysis

The main objective of the present study was to stratify HD gene-expansion carriers into subgroups that share patterns of longitudinal psychiatric trajectories. To achieve this goal, we implemented an adapted version of the Disease Trajectories unsupervised clustering as recently demonstrated in Giannoula et al. (2024). Amongst other adaptations for cost-minimization and user-defined flexibility (see Giannoula et al. (2024) for details), the current approach expanded on earlier unsupervised-clustering methodology by incorporating a numerical dimension. This thereby enabled the study of three-

dimensional clinical data, where each patient trajectory was defined by (1) the participant, (2) time, and (3) PBA-s score at each point in time. In other words, this framework quantifies individual differences in psychiatric features across the four domains (i.e., depression, irritability, apathy, dysexecutive behaviors) at each point in time across a range of degrees of severity.

For context, the Disease Trajectories analysis software utilizes dynamic time warping (M. Muller, 2007) to group a collection of temporal sequences (e.g., longitudinal psychiatric scores), according to shared temporal characteristics, regardless of differences in time scales, overall sequence lengths, and/or differing inter-assessment intervals. Effectively, this non-linearly aligns ('warps') temporal sequences to minimize the accumulated distance between the two trajectories across all points in time (**Figure 7.1A**). This property of dynamic time warping renders it well-suited to identify similarities between HD trajectories that may otherwise conceal underlying patterns in psychiatric severity and evolution, without relying on *a priori* models of time.

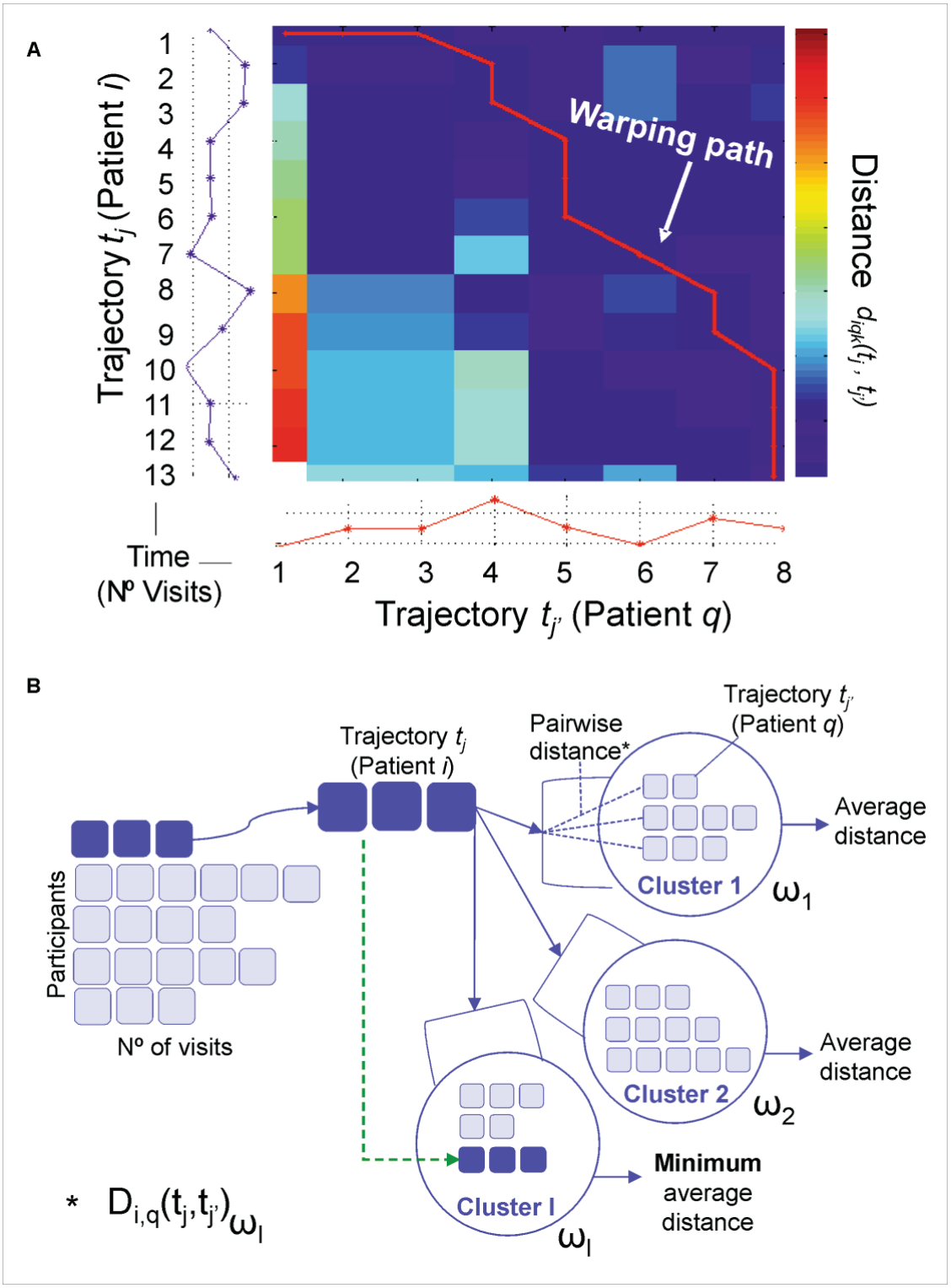


Figure 7.1. Alignment of temporal sequences with dynamic time warping highlights psychiatric trajectories. (A) The accumulated distance along the warping path of the distance matrix is utilized to **(B)** cluster patients with shared psychiatric severity across time (i.e., similarities in psychiatric severity across a range of time points). $d_{iqk}(t_j,t_{j'})$ = individual distances between two participants; $D_{i,q}(t_j,t_{j'})_{\omega l}$ = absolute distance of associated attributes; i = first individual; k = attribute variables (psychiatric features) assigned at this time; l = cluster number; Nº = number of visits; q = second individual; t_j = trajectory of discrete times for first individual; $t_{j'}$ = trajectory of discrete times for second individual; ω = attribute weighting.

In brief, the Disease Trajectories analysis software incorporates two user-defined parameters, *lambda* (*λ*) and *threshold* to guide the clustering process. First, *λ* controls the balance between using more or fewer score attributes for clustering, wherein a lower value of *λ* distributes weights across fewer features, resulting in fewer features being considered. This parameter assigns a weight (%) to each of the four psychiatric domains. The highest weight, expressed as a percentage, is assigned to the feature with the smallest dispersion between trajectory X and trajectory Y. In the present study, the assigned weight revealed the contribution of each of the four psychiatric features to a given cluster (Friedman & Meulman, 2004). For each iteration of the clustering algorithm, the attribute weights were recalculated for each cluster, and the minimum averaged distance between each new psychiatric trajectory and the trajectories previously assigned to each cluster was sought (see **Figure 7.1B**).

Second, the *threshold* parameter is used to determine whether trajectory X is sufficiently similar to the current cluster for inclusion, or if it should instead form the first trajectory in a new cluster. In other words, the *threshold* parameter controls the granularity of clustering, with lower values resulting in more homogenous but potentially more fragmented clusters (high granularity), while higher values of *threshold* permit less homogenous but larger clusters (low granularity).

In the present study, the aim was to generate clusters that were sufficiently homogeneous without excessive fragmentation, to enhance clinical relevance and generalizability of the results. Therefore, an optimum combination of *threshold* and *λ* was selected by minimizing the average mean distance across all clusters, simultaneously satisfying the criteria of (i) keeping the average mean distance below 30% of the maximum mean distance, and (ii) limiting the number of clusters with only one participant to 25% of the maximum number of clusters. Values of *λ* and *threshold* were sequentially assessed, ranging from 0.01 to 1 in increments of 0.01 for *λ,* and from 0.25 to 8 in increments of 0.25 for *threshold*. For methodological details, refer to Giannoula et al. (2024).

As such, sensitivity analyses (of the domain-wide category) were effectively carried out through this cluster evaluation algorithm developed in parallel. Specifically, by considering a wide range of the two input parameters (*λ* and granularity *threshold*), we assessed the performance of the entire clustering methodology in terms of the total

averaged heterogeneity (compactness), as shown in **Figure 7.2** (heatmap) and described in more detail in Giannoula et al. (2024).

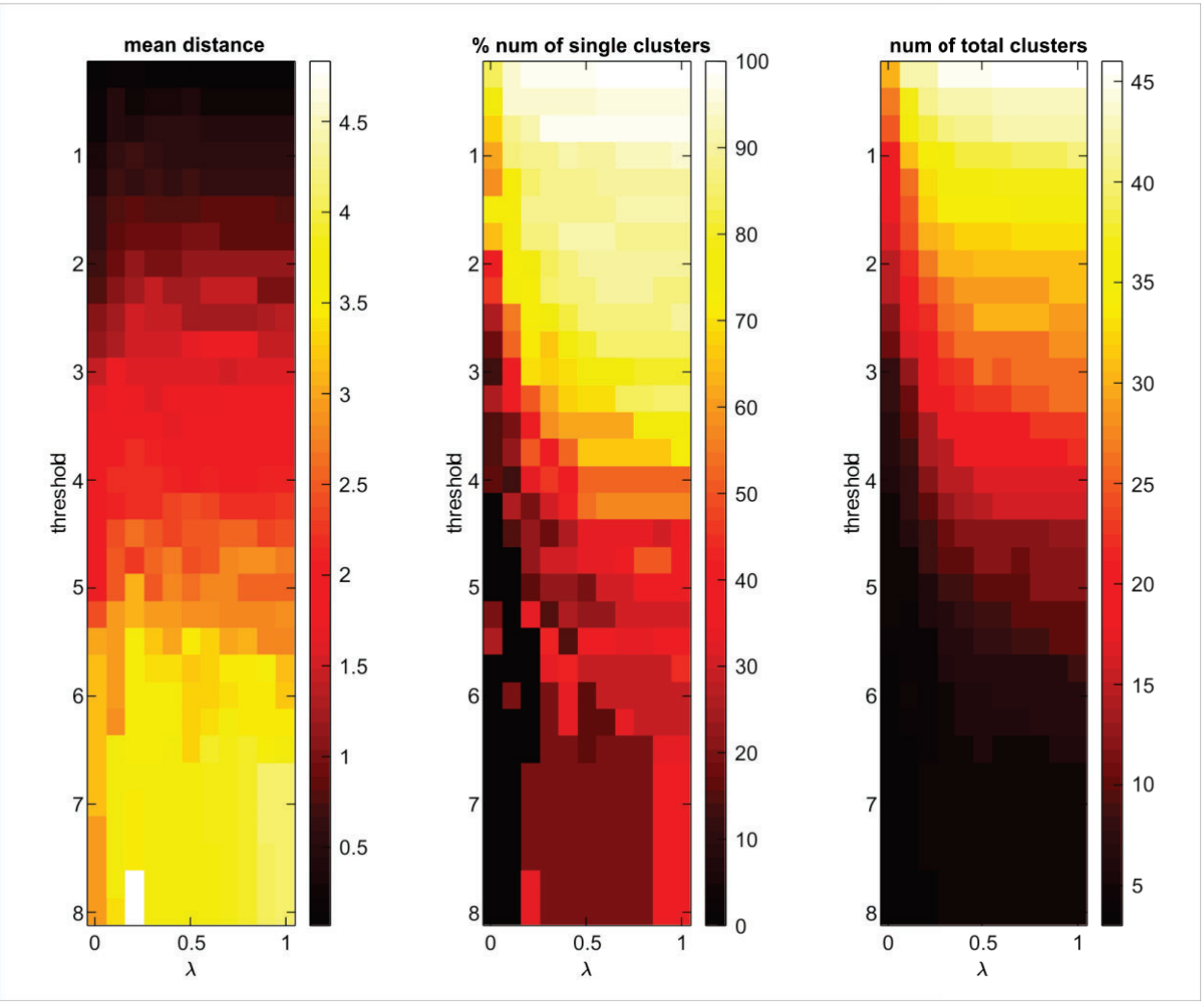


Figure 7.2. Heatmaps depicting clustering performance at sequential combinations of λ and *threshold* values ($0.01 \leq \lambda \leq 1$ by 0.01; $0.25 \leq$ *threshold* ≤ 8 by 0.25). The optimum combination of λ and *threshold* ($\lambda = 0.01$, *threshold* = 2.75) produced an average mean distance across all clusters of 1.12.

7.2.3 Statistical Analyses

Linear fits were calculated for PBA-s scores within trajectories containing ≥ 3 time points for each cluster, using the *polyfit* function in MATLAB (MATLAB R2019b, MathWorks, Natick, MA). The analysis was focused on the largest clusters that exhibited shared patterns of longitudinal psychiatric trajectories, collectively explaining ≥ 50% of the sample. We further explored and characterized group differences in the selected clusters.

Continuous variables (demographic and clinical data, including psychiatric features, number of visits) were compared with the Wilcoxon rank-sum test, while categorical variables (diagnostic status, sex, on/off specified medications) were compared with the two-sided Fisher's exact test. Phenoconverters, defined as those individuals who transitioned from premanifest to manifest over the course of the study, were excluded from the analysis of group differences related to diagnostic status. Additionally, Spearman correlations were performed to assess associations between pertinent average psychiatric features (e.g., apathy with dysexecutive behaviors). For significant results, effect size was reported (e.g., Wilcoxon effect size (r)). All group-level analyses were carried out using R (v.4.1; R Foundation for Statistical Computing, Vienna, Austria).

Correction for multiple comparisons, where applicable, was performed using the false discovery rate (q = 0.05), with the number of comparisons specified in the text. Both raw P-values (P) and the P-adjusted false discovery rate values (P-adj) are reported. Differences were considered statistically significant when P-adj ≤ 0.05.

7.3 Results

7.3.1 Shared Psychiatric Trajectories

Unsupervised clustering resulted in eleven clusters representing distinctive longitudinal trajectories of psychiatric features over time (**Figure 7.3; Table 7.2**). The contribution of each psychiatric domain to each cluster was examined based on the λ-assigned weights (**Table 7.2**). The optimum combination of λ and *threshold* was determined by minimizing the average mean distance across all clusters, indicating increased overall intra-cluster homogeneity and improved performance of the clustering algorithm. The optimal combination was found to be λ = 0.01 and *threshold* = 2.75, resulting in an average mean distance = 1.12 across all eleven clusters (**Figure 7.2**).

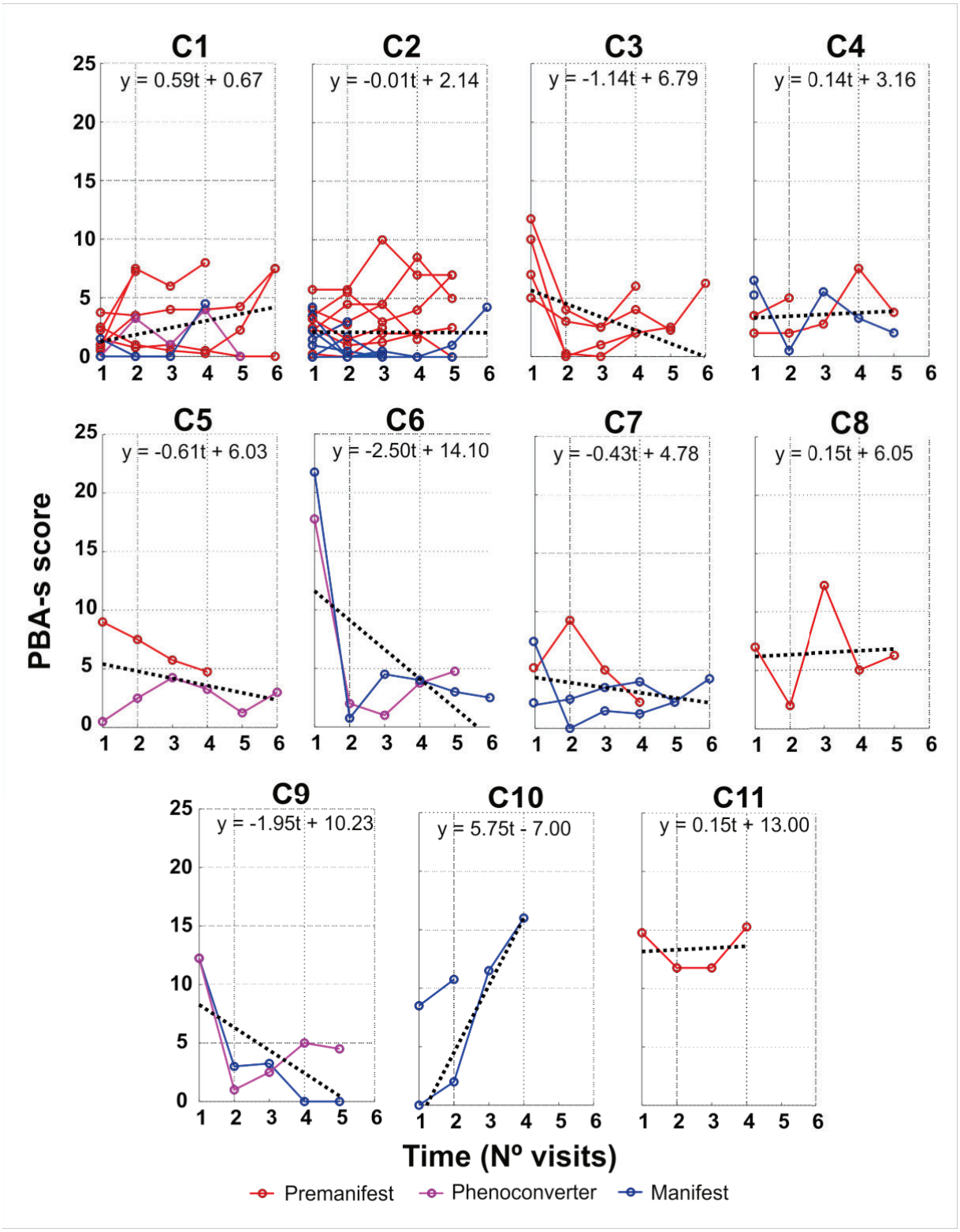


Figure 7.3. Unsupervised clustering produced eleven clusters, each representing a distinct psychiatric trajectory over time. C = cluster; PBA-s = short-Problem Behaviors Assessment.

Table 7.2. Cluster metrics of shared psychiatric evolution

Cluster	*N*	*N**	Mean distance	Slope	Domains†			
					Depression	Irritability	Apathy	Dysexecutive Behaviors
1	10	39	1.11	2.355	**0.87 ± 1.11**	2.56 ± 1.60	2.54 ± 2.30	3.50 ± 2.01
2	15	58	0.45	-0.049	3.59 ± 2.30	**0.14 ± 0.46**	3.36 ± 1.94	2.98 ± 1.74
3	4	19	1.77	-4.543	2.62 ± 1.87	**2.88 ± 3.31**	5.15 ± 2.42	4.67 ± 2.03
4	4	13	1.24	0.550	6.05 ± 2.73	2.90 ± 1.00	3.15 ± 2.26	**4.55 ± 0.94**
5	2	10	0.84	-2.457	6.96 ± 1.95	**1.46 ± 0.02**	6.92 ± 0.07	3.08 ± 0.04
6	2	11	1.00	-9.993	5.97 ± 2.02 (0.1)	6.08 ± 1.54	6.63 ± 0.62	**5.18 ± 1.39 (99.1)**
7	3	15	1.49	-1.724	7.26 ± 3.12	3.43 ± 1.85	**1.30 ± 1.08**	2.64 ± 1.89
8	1	5	0.00	0.600	11.60 ± 0.00 (25)	6.20 ± 0.00 (25)	3.60 ± 0.00 (25)	4.60 ± 0.00 (25)
9	2	10	1.21	-7.800	8.40 ± 2.19	1.80 ± 1.80	4.10 ± 1.14 (6.7)	**3.20 ± 0.57 (93.3)**
10	2	6	0.97	23.00	12.63 ± 7.79	4.75 ± 2.34	**5.13 ± 2.52**	11.50 ± 5.55
11	1	4	0.00	0.600	21.75 ± 0.00 (25)	1.00 ± 0.00 (25)	14.00 ± 0.00 (25)	7.75 ± 0.00 (25)

A lower mean distance denotes increased overall intra-cluster homogeneity. *N* = number of participants; *N** = number of data points. †Domains presented as *mean ± standard deviation (weight, where differing from 0 or 100)*. Average values are across all time points and all participants per cluster. Weight is indicated as a percent. Domain with highest weight in each cluster is displayed in **bold**, where applicable.

7.3.2 Group Differences in Psychiatric Trajectories

Two main psychiatric signatures (C1, C2) were identified, collectively explaining 54% of the total sample and encompassing 10 and 15 participants, respectively (**Figure 7.4A**). As these clusters explained the majority of the sample, they were further evaluated to reveal specific psychiatric features that distinguish and characterize them. In particular, C1 showed an increase in overall behavioral abnormalities over time, as evidenced by the positive slope (**Figure 7.4B; Table 7.2**). On the other hand, C2 demonstrated a constant persistence of psychiatric features over time. There was no significant association between premanifest ($N_{C1} = 2$; $N_{C2} = 7$) or manifest ($N_{C1} = 7$; $N_{C2} = 8$) diagnostic status and assigned clusters for these two psychiatric trajectories ($P = 0.390$).

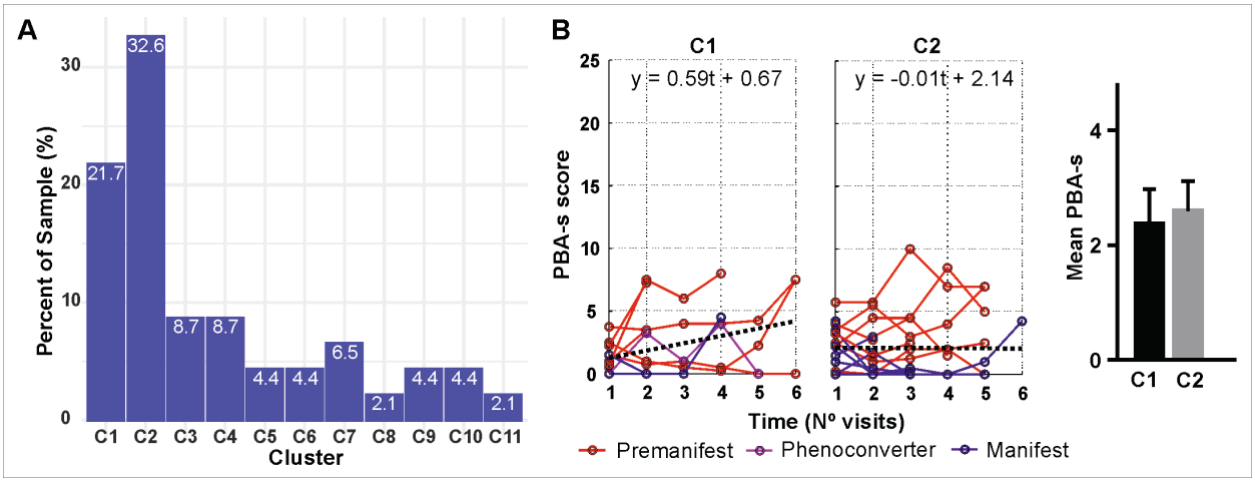


Figure 7.4. Psychiatric signatures in the two main clusters differ in overall behavioral abnormalities. **(A)** Percent of the sample explained per cluster, with two main clusters explaining 54% of the total sample. **(B)** C1 demonstrates an increase in average PBA-s scores, while C2 exemplifies persistent development. C = cluster; PBA-s = short-Problem Behaviors Assessment.

The λ-assigned weights revealed that the psychiatric signatures of C1 and C2 were primarily characterized by a dissociation in the longitudinal trajectories of depressive and irritable features (**Table 7.2**). Specifically, C1 showed a pattern of non-depression with increasing irritability (**Figure 7.5A,B**). Conversely, C2 presented non-irritability coupled with an initial increase followed by a subsequent decrease in depression (**Figure 7.5A,B**). Both clusters showed an increase in apathy and dysexecutive behaviors (**Figures 7.5C,D**).

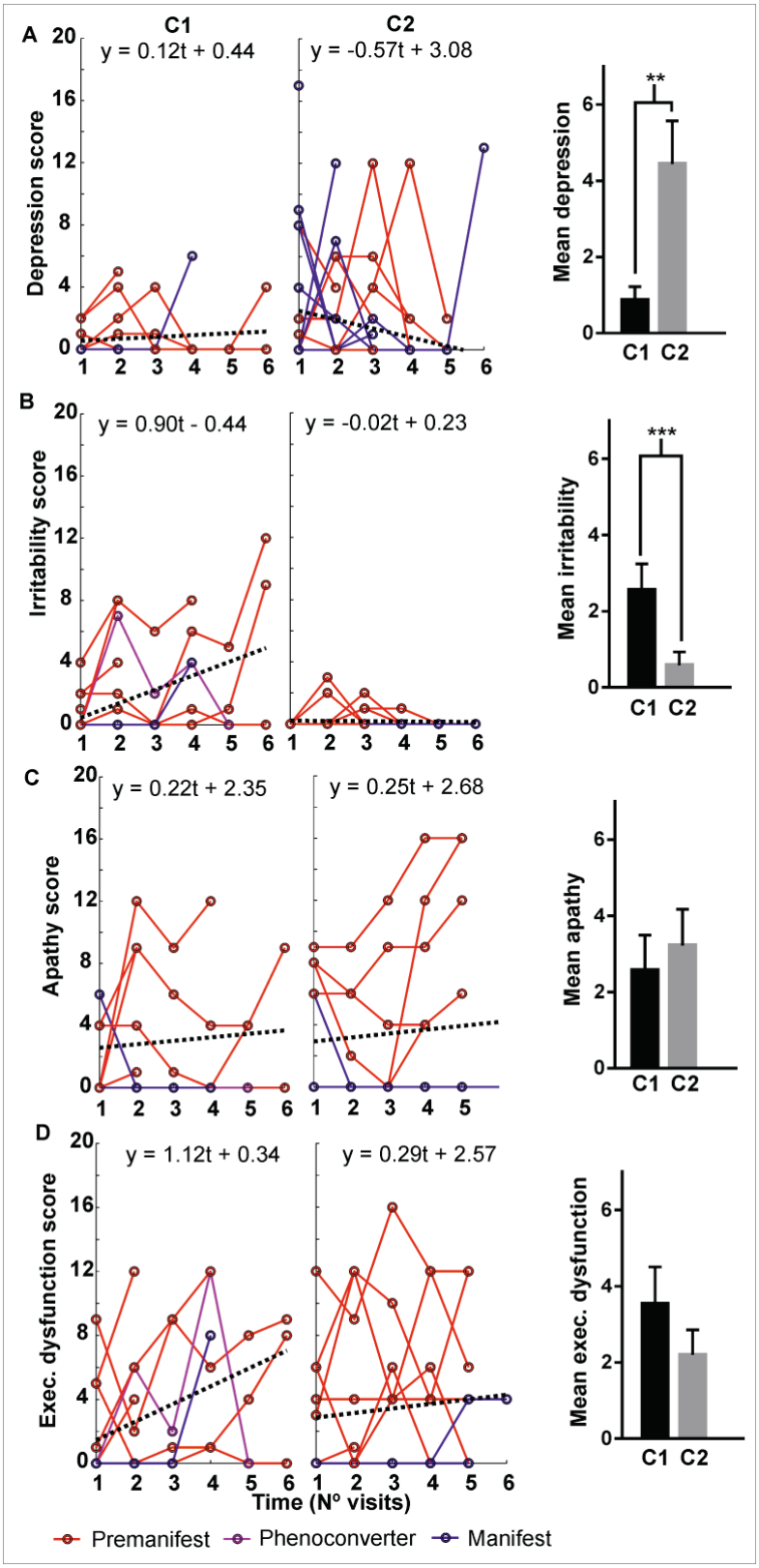


Figure 7.5. Psychiatric signatures are defined by unique trajectories in specific domains. C1 was defined by a trajectory of **(A)** non-depression with increasing irritability, while C2 presented a trajectory of **(B)** non-irritability with rise-and-fall depression. Both clusters increased in **(C)** apathy and **(D)** dysexecutive behaviors over time. ***P*-value < 0.01, ****P*-value < 0.001 after controlling for multiple comparisons. C = cluster.

Subsequently, the two main clusters were examined for group differences in the overall severity of psychiatric features (**Figure 7.5**). As expected, there was a significant difference in mean depression (Z = -2.70; P = 0.007, *P-adj* = 0.014) and irritability (Z = -3.51; P < 0.001, *P-adj* = 0.002) between the two clusters, but not in apathy and dysexecutive behaviors (four comparisons). A large effect size was observed for both depression (|r| = 0.54) and irritability (|r| = 0.70). Notably, the average value of apathy and dysexecutive behaviors was deemed clinically relevant by the predefined cut-off. To further investigate these findings, correlations were performed between apathy and dysexecutive behavior scores in both clusters (two comparisons; **Figure 7.6**). A significant positive relationship of strong effect was found in both C1 (r_s = 0.708, P = 0.022, P-adj = 0.022) and C2 (r_s = 0.673, P = 0.006, P-adj = 0.012). There were no significant baseline or average differences in CAP, years of education, or UHDRS motor or cognitive scores. Sex and medication use also did not differ between the two main clusters, nor did the number of visits.

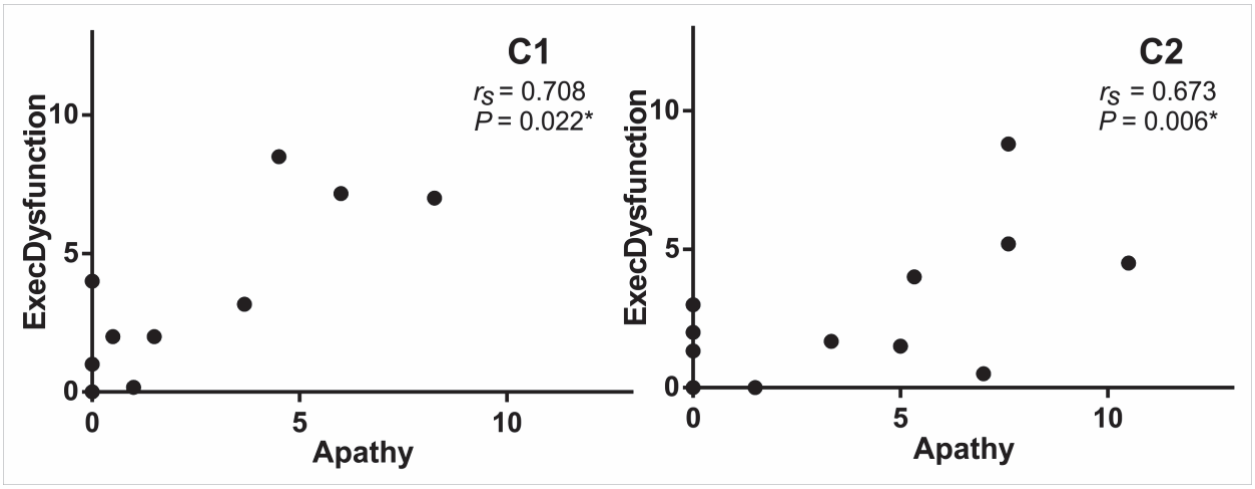


Figure 7.6. Apathy and dysexecutive behaviors are positively correlated, as demonstrated in both C1 and C2. *P-value survives false discovery rate correction at q = 0.05. C = cluster.

7.4 Interpretation

This exploratory study aimed to characterize longitudinal psychiatric signatures in HD gene-expansion carriers, identifying shared and clinically relevant disease trajectories among subgroups. In total, eleven clusters were identified, with two main psychiatric signatures comprising the majority of the sample. Both main clusters showed a dissociation between depression and irritability. The first cluster (i.e., longitudinal

trajectory) was characterized by non-depression with increasing irritability, while the second cluster exhibited non-irritability alongside a rise-and-fall in depression, in that depression initially increased in earlier phases of the disease and later decreased. Apathy and dysexecutive behaviors were clinically relevant in both cohorts, with overall severity increasing over time. Importantly, these identified groups included both premanifest and manifest individuals, highlighting the heterogeneity in specific psychiatric patterns that may arise prior to motor onset in HD and be shared by individuals later in the disease course.

The two main psychiatric signatures showed differences in both the severity and the evolution of the overall psychiatric symptoms. Participants following the non-depressive + irritable trajectory exhibited an overall longitudinal increase in psychiatric disturbances predominantly characterized by frontal behaviors, specifically dysexecutive functioning. The coupling of obsessive-compulsive and other dysexecutive behaviors with the absence of depression is in line with previous findings in premanifest individuals (Paulsen et al., 2014).

On the other hand, those with the non-irritable + rise-and-fall depressive trajectory maintained a persistent level of psychiatric dysfunction over time. High baseline levels of behavioral dysfunction that remain constant over time have been previously reported in HD (The Huntington Study Group PHAROS Investigators et al., 2016). Meanwhile, the rise-and-fall pattern of depression over time, where higher levels of depression are present in early phases of the disease with a decrease in later phases, is in concordance with previous research. For instance, depression has been shown to appear during the premanifest stage, reach a peak near early manifest stage 2, and then resolve in later manifest stages (Epping & Paulsen, 2011; Paulsen et al., 2005). Other studies have consistently evidenced that depression severity in HD is unrelated to CAG-expansion length or time since genetic testing, and may occur at any point during the course of the disease (Duff et al., 2007; Epping et al., 2013; Zappacosta et al., 1996).

In the current literature, the relationship between depression and irritability in HD yields inconsistent findings. For example, although some studies have suggested a positive correlation between depression and irritability (Litvan et al., 1998; Nimmagadda et al., 2011; van Duijn et al., 2014), others have demonstrated no relationship (Bouwens et al.,

2015) or an association of poor strength (van Duijn et al., 2018). While the observed heterogeneity may be compounded by non-standardized rating scales and the use of composite scores for psychiatric dimensions, such variability may also be explained by an undercurrent of individual differences in the patterns of disease progression, which warrant evaluation.

Furthermore, the trajectories of specific psychiatric domains also differed between groups. The non-depressive + irritable group revealed a steady increase in irritability. This is in line with previous research indicating that irritability and hostility tend to worsen over time in HD (Craufurd et al., 2001; Kirkwood et al., 2002). Moreover, irritability has been shown to be positively associated with worsening motor symptoms in both premanifest and manifest HD (van Duijn et al., 2013) as well as apathy, a psychiatric feature which has been consistently shown to track disease progression (Bouwens et al., 2015; Fritz et al., 2018). Other studies have posited irritability as a marker of HD progression and a significant feature of the HD process, manifesting both before and after the formal diagnosis at motor onset (Simpson et al., 2019; Tabrizi et al., 2009). At the same time, not all patients exhibit irritability (Bouwens et al., 2015), and some may even experience a decrease in irritability with increasing atrophy (Singh-Bains et al., 2016). This point underscores the need for individual-level analysis focusing on subgroups of patients that may show differing trajectories of psychiatric evolution.

There is still debate regarding whether certain psychiatric symptoms, particularly depression, are due to neurobiological changes or merely represent a reactive response to being at risk for HD (Rosenblatt, 2007; Ross et al., 2019). However, even when blinded to CAG-expansion status, premanifest individuals were found to exhibit significantly higher prevalence and severity of depression and irritability at baseline compared to at-risk individuals without the expansion. Moreover, they are almost twice as likely to report depressive disorder compared to non-carriers (Julien et al., 2007; The Huntington Study Group PHAROS Investigators et al., 2016). Additionally, several neurologic correlates have been associated with depression in HD at the metabolic, neuronal, and functional level, further supporting the link between depression and the neurodegenerative disease process (Krogias et al., 2011; Mayberg et al., 1992; Tippett et al., 2007; Unschuld et al., 2012). Neurochemically, selective inhibition of monoamine oxidase restored dopamine,

serotonin, and norepinephrine neurotransmitter levels in the striatum in a mouse model of HD (Garcia-Miralles et al., 2016), which was behaviorally coupled to improved anxiety and less depressive behaviors in affected mice (Garcia-Miralles et al., 2016). These findings suggest that psychiatric features in HD cannot be simply attributed to living in a family affected by HD or concerns about developing the disease, but rather is at least partially related to the genetic mutation itself.

Both clusters exhibited clinically relevant apathy and dysexecutive behaviors that worsened over the course of the disease. These findings are consistent with previous research showing that both apathy and obsessive-compulsive behaviors (i.e., executive dysfunctions) have been shown to increase as HD progresses, and are associated with reduced functional capacity (Anderson et al., 2010; Beglinger et al., 2007; Craufurd et al., 2001; Kingma et al., 2008; Paoli et al., 2017; Tabrizi et al., 2013; van Duijn et al., 2014). Importantly, this relationship is upheld even when controlling for progressive motor and cognitive deficits (Hamilton, 2003). In a similar vein, among the emotional disturbances typically observed in HD, changes in apathy and dysexecutive behaviors portray the most robust effect sizes in severity over time when compared to other psychiatric signs such as hostility, depression, and anxiety (Paulsen et al., 2014).

Taken together, apathy and dysexecutive behaviors are hallmark psychiatric features in fronto-subcortical disorders such as HD (Rosenblatt, 2007). These features involve deficits in regions such as the OFC, dlPFC, and ACC (De Paepe et al., 2019, 2021). In fact, apathy and executive dysfunction demonstrate a high inter-correlation as frontal lobe behavioral changes in HD (Hamilton, 2003). For this reason, the co-occurrence of apathy and domains of dysexecutive behaviors (i.e., perseveration, obsessions, compulsions) in HD is recognized as a consistent clinical manifestation (Rickards et al., 2011; Sellers et al., 2020). Interestingly, apathy and dysexecutive behaviors were found to be better predictors of unemployment in HD than motor performance (Jacobs et al., 2018). Nonetheless, it is worth noting that there is currently no gold-standard treatment for apathy, and more research is needed in this area (Mason & Barker, 2016).

Lastly, it is notable that the two main cohorts included individuals at premanifest and manifest stages. This aspect is particularly interesting, as it exemplifies the potential of the current framework to forecast the trajectory that a premanifest individual may

develop. For example, individuals with a lower disease burden in a given cluster may exhibit a psychiatric signature similar to patients in the same cluster who are further along in the disease process.

In the literature, the categorization of premanifest and manifest stages has long been regarded as a false dichotomy concerning the psychiatric symptoms (Ross et al., 2014). In some contexts, the monosymptomatic diagnosis of HD based solely on motor features is considered outdated (Epping et al., 2016). In fact, when CAG-expansion carriers were diagnosed according to multidimensional criteria that incorporated behavioral, cognitive, and functional dimensions in addition to motor signs, 37.1% of participants received an HD diagnosis at an earlier time than when diagnosis was based solely on motor examination (Biglan et al., 2013). Moreover, these individuals showed significantly lower motor and cognitive deterioration, but not behavioral dysfunction, compared to those who received the multidimensional and classical motor diagnosis simultaneously.

The fact that this study revealed eleven distinct trajectories of psychiatric evolution underscores the heterogeneity within the disease. Moreover, it highlights the necessity to establish specific methodological frameworks for patient stratification in psychiatric and, more broadly, clinical domains, as previously emphasized (Dwyer et al., 2018; Segalàs et al., 2024). These approaches allow the stratification of seemingly homogeneous groups and facilitate the development of specific biomarkers for predicting prognosis as well as treatment response in clinical trials, even across diagnostic boundaries.

Despite these advancements, most longitudinal studies in HD have largely focused on group differences defined *a priori* based on diagnostic status (Tabrizi et al., 2013) or the probability of impending motor diagnosis (Epping et al., 2016; Paulsen et al., 2014). This has led to calls for the modification of current diagnostic criteria to incorporate psychiatric features (Reilmann et al., 2014; Ross et al., 2019). An earlier characterization of HD in both prodromal (i.e., symptomatic premanifest gene-carriers) and manifest stages would enable a personalized and preemptive treatment approach (McColgan & Tabrizi, 2018). Specifically, disease-modifying therapies may be administered during an optimal window, before the disease has significantly progressed, allowing for potential forestalling or even reversal of neurodegeneration (Caron et al., 2018; Siebzehnrübl et al., 2018; Yamamoto et al., 2000). This underscores the need for an expanded focus of

machine learning in the study of psychiatric features of HD in both clinical care and research.

In an effort to address this gap in the literature, the present methodology highlights the potential of the Disease Trajectories Analysis Software (Giannoula et al., 2024) to harness three-dimensional clinical data with longitudinal and numerical dimensions. The promising outcome of generating optimized clusters with clinically relevant findings using a relatively small sample size demonstrates the versatility of this methodology for application in small and large patient cohorts and rare diseases, with future applications in multi-center studies. A key strength of this approach lies in its freedom from the need of an *a priori* definition of the number of clusters, absence of assumptions of data normality, and flexibility not confined to a predefined model (e.g., linear) of how the trajectory will vary over time, setting it apart from other machine learning models such as growth mixture modeling (Kwon et al., 2021; Riglin et al., 2019). Overall, the ability to identify fundamental time patterns as well as deviating or even "outlier" clusters constitutes a strength of our approach, especially in the field of neuroscience where heterogeneity is very often seen at the individual level even for patients with the same disease label.

Ultimately, the existence of this longitudinal data-mining methodology has great potential for improved understanding of diseases, yet few studies are taking advantage of this approach to date. Future research harnessing the Disease Trajectories approach has the potential to bridge a gap in the literature and provide new insights into why patients with seemingly similar demographics and clinical onset may exhibit variable disease progression. The application of the Disease Trajectories analysis software in larger, multicenter HD studies, such as Enroll-HD or REGISTRY (Landwehrmeyer et al., 2016; van Duijn et al., 2014), bears promise in delineating additional HD trajectories across psychiatric, cognitive, or motor domains. Further applications may include identifying the neural signatures associated with each psychiatric trajectory using neuroimaging, which can also be incorporated into the present algorithm (Giannoula et al., 2024).

The current study presents certain limitations that need to be considered. First, the sample size is notably small, and further work should replicate this methodology in larger HD datasets, as aforementioned. Next, while the PBA-s has shown substantial inter-rater

reliability (Callaghan et al., 2015), the majority of single-item components of the PBA-s have not been assessed for reliability (Sellers et al., 2020). To address this limitation, we used composite domain scores (Landwehrmeyer et al., 2016), for which there is general consensus in the field (Callaghan et al., 2015; Rickards et al., 2011; Ruiz-Idiago et al., 2017). Future investigations may consider sub-features of psychiatric dimensions, such as internal vs. external expressions of irritability, which may differ in individuals with depression (Simpson et al., 2019). Another concern is that, while medication intake was considered, individual patients may respond differentially to the same treatment. While there is currently no established gold-standard treatment for apathy in HD, depression and irritability can be effectively managed with pharmacological agents, even in premanifest HD (Eddy et al., 2016; Ross et al., 2019). However, it should be noted that individual patients may respond differentially to the same treatment (Zielonka et al., 2015). Medication regimens and variability in treatment response may impact the expression and progression of the psychiatric disorders and should be a focus of future investigation. Additional research questions could also consider the impact of environmental factors on psychiatric dysfunction, such as substance use. Future research that incorporates longitudinal assessment of treatment response has the potential to not only control for these factors, but also provide insights into preferential medication regimens for distinct psychiatric signatures that may react differently to the same medications.

In conclusion, this work identifies distinct psychiatric trajectories in HD, highlighting a dissociation between irritability and depression that was revealed through longitudinal multivariate analysis of their progression over time. Of the two main trajectories, the first was defined by increasing irritability, no depression, and an overall longitudinal increase in psychiatric disorders over time; the second demonstrated no irritability and a rise-and-fall in depression coupled with stable persistence of behavioral disorders. In this way, these findings underscore that the observed heterogeneity in psychiatric subdomains across HD studies may be partially explained by the existence of subgroups with distinct longitudinal signatures. These trajectories may be shared by premanifest and manifest individuals, with implications for more personalized prognosis for those early in the disease course.

In this way, the present framework sheds light on the interrelation between distinct psychiatric domains, with potential to predict which profiles may develop more severe disease trajectories over time. Such work may aid in the designation of more homogenous patient subgroups for clinical trials, allowing more precise evaluation of treatment success or failure. Ultimately, this proof-of-concept study acts as a model for investigating distinct patterns of clinical and biomarker progression in patient populations, with the aim of better personalizing prognostic indicators and therapeutic interventions in both curated and multicenter data sets.

Chapter 8
Discussion

Chapter 8 | Discussion

The overarching aim of this Doctoral Thesis was to describe apathy as a multidimensional construct in HD, while investigating its structural neurobiological underpinnings and longitudinal relationship with associated psychiatric features of the disease. Until the present body of work, no study had empirically examined the neurobiological correlates of apathy dimensions in HD, and studies in other neurodegenerative populations are limited. This Doctoral Thesis thus takes a step beyond the current literature by not only investigating apathy dimensions using a combination of clinically valid instruments in HD, but also investigating the structural neural correlates of apathy and its interrelation with other psychiatric features both cross-sectionally and longitudinally.

This body of work provides evidence that apathy can be characterized as a multidimensional construct in HD using the LARS-s, a scale we demonstrated to be valid and reliable in this patient population (**Research Aim 1**). Next, distinct apathy dimensions were found to be represented by unique neural signatures. This included disruption in WM microstructural connectivity in specific frontostriatal circuits and reduced GMV across large-scale motor, cognitive, and limbic territories (**Research Aim 2**). In addition, more severe and rapid progression of apathy over time was predicted by initial vulnerabilities in GMV in an integratory hub, the right MCC (**Research Aim 2** and **3**). Lastly, the longitudinal progression of global apathy was related with dysexecutive behaviors and discrete psychiatric trajectories in HD (increasing irritability and rise-and-fall depression) (**Research Aim 3**).

This chapter comprises a concise summary of the main findings of the current Doctoral Thesis in relation with the Research Aims. Given the incipient nature of the study of apathy dimensions in HD, the Discussion is situated in the context of multidimensional apathy in neurodegenerative disease, both within and beyond HD. In addition, possible clinical applications are highlighted in light of the present findings. To close, limitations are acknowledged and future directions proposed.

8.1 Summary of Results

Study 1 provided evidence that apathy subdimensions, as deconstructed from the LARS-s, were represented by individual differences in WM microstructural (dis)connectivity in HD. First, global apathy was the most common of eleven psychiatric disturbances, with a prevalence of 45% amongst the combined premanifest and manifest HD sample. The LARS-s was then decomposed into three dimensions (i.e., cognitive, emotional, and auto-activation). Both auto-activation deficit and cognitive apathy were found to be higher in manifest individuals than in healthy controls. Indeed, auto-activation deficit was higher even in premanifest individuals alone compared to controls. This was not true for global apathy in premanifest individuals, in which no significant differences were observed, suggesting that certain apathy subdimensions may be more sensitive to the onset of apathetic behavior early in the disease course. In further substantiation of the above results, global apathy, cognitive apathy, and auto-activation deficit, but not emotional apathy, were significantly associated with measures of disease burden.

Similar to the behavioral results, the relationship between disrupted microstructural connectivity of discrete WM tracts and apathy dimensions was specific for cognitive apathy, auto-activation deficit, and global apathy. In particular, severity of cognitive apathy was related with increased MD (a proxy of reduced connectivity) in the right FST and left dlPFC-cn. Meanwhile, more severe auto-activation deficit was linked with increased MD (reduced connectivity) in the right UF. Lastly, greater MD in the right FST and right UF was related with globaly apathy severity. Overall, these findings provided evidence that WM dysfunction in discrete cortico-striatal tracts may modulate the heterogeneous nature of apathy in HD.

Next, **Study 2** highlighted that individual differences in global apathy severity and progression in HD may be explained by variability in brain atrophy over time and initial vulnerabilities specifically in the right MCC, an area implicated in action-initiation. At baseline, clinically significant apathy was apparent in 47.8% of the combined HD sample and correlated with a marker of disease state that has been related with HD progression. Longitudinal data revealed that 64.4% of individuals manifested clinical levels of global apathy at some point during the course of the study, with only 26.7% not expressing even

mild signs of apathy. Neurobiologically, greater apathy was significantly related with a larger reduction in GMV specifically in the right MCC (BA 24). These results were specific to apathy; neither depression nor cognitive scores were related with volume loss in this region. Meanwhile, supplementary cross-sectional results revealed that global apathy severity was associated with reduced GMV in cortical and subcortical areas, including the left MCC, right SMA, bilateral dlPFC, left insula, right inferior parietal lobe, and the bilateral pallidum, putamen, and caudate head.

Subsequently, generalized linear mixed-effects models elucidated that initial and specific MCC vulnerability successfully predicted the overall severity and longitudinal progression of apathy at the individual level. In brief, initial vulnerability (i.e., smaller volume) in the right MCC predicted those individuals who were more likely to develop apathy or experience worsening apathy at a future point in time. By extension, initial MCC volume additionally informed a prognosis of worsening cognitive outcomes, but not depression. Lastly, longitudinal cognitive scores (but not depression) predicted apathy progression over time. These findings evidence that specific regional vulnerabilities may facilitate the prediction of an apathetic profile in HD, permitting targeted, time-sensitive interventions in neurodegenerative disease.

Study 3 empirically demonstrated that the LARS-s exhibits satisfactory psychometric properties and is capable of capturing the multidimensional spectrum of apathy in HD. Specifically, the LARS-s demonstrated reliability (internal consistency) as well as convergent validity with apathy and discriminant validity with depression. Principal component analysis of the seven LARS-s domains resulted in three factors in accordance with the three-dimensional model of apathy: cognitive apathy (daily productivity and interest), auto-activation deficit (initiative and motivation), and emotional apathy (emotional responses and novelty seeking). In addition to auto-activation deficit, the initiative domain partially loaded on the cognitive apathy dimension. The social life domain had a low extraction communality value and lower component loadings across all three dimensions.

At the same time, this study revealed that apathy profiles in HD are underpinned by reduced GMV in nodes within functionally diverse neural networks. To start, global apathy demonstrated a significant negative relationship with GMV in the left middle

temporal lobe, right ACC extending to the dlPFC, and left superior temporal pole extending to the insula. Exploratory thresholds revealed further associations between global apathy and frontostriatal and inferior-parietal networks encompassing cortical and subcortical regions, including the SMA and OFC. Regarding apathy dimensions, greater cognitive apathy was significantly linked with decreased GMV in the left inferior-parietal lobe and the dmPFC, specifically the right SMA extending to the right MCC, with nonsignificant associations in the middle temporal lobe and thalamus. Meanwhile, auto-activation deficit was associated with cortical and subcortical regions across cognitive and motor territories, including the right lingual gyrus (significant), bilateral putamen, dlPFC, and middle temporal areas. Lastly, emotional apathy was associated with ventral and middle frontal areas of limbic functioning, including the insula and ventral ACC. In general, such findings promote the continued study of apathy dimensions using the LARS-s, a scale capable of capturing apathy's underlying sub-architecture, to pinpoint personalized therapeutic targets.

Finally, **Study 4** utilized a novel machine-learning approach to perform unsupervised clustering of longitudinal psychiatric trajectories. The clustering analysis with optimum performance revealed eleven clusters, each representing a distinctive signature of shared psychiatric features over time. There was no significant difference in the number of participants with premanifest and manifest diagnostic status within the two main psychiatric signatures (i.e., clusters). The first cluster showed a pattern of increasing overall behavioral abnormalities, increasing irritability, and no depression. The second cluster showed constant persistence of overall behavioral abnormalities, with rise-and-fall depression and no irritability. Importantly, the trajectories of apathy and dysexecutive behaviors (i.e., perseveration and obsessive-compulsive behaviors) increased and significantly correlated in both clusters. Ultimately, through the delineation of individual-level psychiatric trajectories with machine-learning, this exploratory study revealed a dissociation of depression and irritability that is apparent even in premanifest stages.

8.2 Apathy is Prevalent and Progressive in Huntington's Disease

Throughout all studies, apathy was shown to be a prevalent and progressive feature of HD. Whether examining apathy cross-sectionally in **Studies 1 and 3** or longitudinally in **Studies 2 and 4**, apathy related with markers of disease state, such as functional capacity, and was found to be more severe and prevalent in manifest than premanifest stages. This work reflects the broader literature, where apathy is regarded as preponderant in HD. Across studies, prevalence estimates range from 23% to 76% (Camacho et al., 2018; Paoli et al., 2017). Taking a closer look, the variability in estimates of apathy prevalence in HD may be influenced by the disease stage studied, as apathy has been consistently shown to increase in later disease stages (Craufurd et al., 2001; Kingma et al., 2008; Tabrizi et al., 2013; Thompson et al., 2012). Nonetheless, this variability is also likely attributable to the lack of a gold standard for apathy measurement. Historically, this has resulted in a wide range of scales used to detect and characterize apathy across studies (Cummings et al., 2024). Additional factors that hinder the investigation of apathy in HD and other neurologic populations include source variability (e.g., patient vs. caregiver assessment) as well as discrepancies in controlling for or excluding dementia and depression.

In the literature, questions have been raised as to whether apathy is an integral part of the biological disease process, or rather a reactionary response to news of the disease or diagnosis (Rosenblatt, 2007; Ross et al., 2019). The progressive nature of apathy in HD, including premanifest stages, substantiates existing evidence that this psychiatric disturbance is not wholly reactionary. Indeed, there is strong evidence that the CAG trinucleotide repeat expansion (e.g., the disease process itself) confers an increased predisposition to develop apathy in HD when compared to otherwise healthy controls. For example, individuals with intermediate-length alleles of CAG repeat expansions (e.g., 27 to 35 repeats) were previously deemed non-pathologic by definition (Potter et al., 2004). However, despite displaying preserved motor, cognitive, and functional abilities, these intermediate expanders were afflicted with greater severity in psychiatric disturbances when compared to controls (Killoran et al., 2013). Specifically, significant differences were observed between individuals with intermediate-length alleles and controls in apathy and suicidal ideation, with non-significant differences in

perseverative/obsessive thinking, depression, anxiety, and irritability. This enjoins better screening and monitoring for these unmet mental health needs. In addition, distinct correlates in brain structure have been unveiled in those with apathy (e.g., GMV, WM microstructure) as displayed in **Studies 1**, **2**, and **3** of this Doctoral Thesis, further supporting the argument that apathy is at least partially a result of HD pathology.

Taken together, the above findings suggest that psychiatric disturbances like apathy in HD cannot be simply attributed to living in a family affected by HD or concerns about developing the disease. Rather, at least in part, apathy is related to the genetic mutation and biological disease process itself, as well as the ensuing neurobiological changes. Further corroborating evidence in HD and other neurodegenerative populations will be examined in subsequent sections of this Discussion.

8.3 Multidimensional Apathy as a Construct

8.3.1 Apathy Profiles in Huntington's Disease

The work encapsulated within this Doctoral Thesis provided some of the first empirical evidence for the existence of apathy as a multidimensional construct in HD. Both theoretically and later empirically through dimension reduction analysis, the results of **Research Aim 1** (**Studies 1** and **3**) support a three-dimensional framework for apathy. Specifically, dimensions were found to align along axes of cognition, auto-activation (i.e., behavioral self-initiation), and emotional responses (R. Levy & Dubois, 2006; Radakovic & Abrahams, 2018). In addition, these studies exemplified that cognitive apathy and auto-activation deficit are the most represented dimensions of apathy in HD. This is in contrast to otherwise healthy individuals, where auto-activation deficit is the least observed (Lafond-Brina & Bonnefond, 2022), putatively because it may be the most severe form and is often associated with neurologically impaired populations.

The presence of multidimensional apathy in HD has since been corroborated, with cognitive and behavioral domains again being the most affected. Similarly using the LARS (although in this case the full-length version), Hendel and colleagues (2021) discovered that manifest HD gene-expansion carriers scored significantly worse than controls on the

intellectual curiosity and action initiation subscales of the LARS as well as the global LARS score (Hendel et al., 2021). In turn, manifest HD individuals significantly differed from premanifest individuals in action initiation, but not intellectual curiosity after correcting for multiple comparisons. There were no significant differences in emotion and self-awareness domains. In contrast to **Study 1**, premanifest individuals did not demonstrate significant differences in any apathy subscales when compared to healthy control participants in this sample (Hendel et al., 2021).

Using the Dimensional Apathy Scale, Atkins and colleagues (2021) revealed that initiation and executive (i.e., cognitive) components of apathy exemplified the greatest prevalence of clinically relevant apathy in manifest HD (34.8% and 30.4%, respectively), with only 15.2% exhibiting emotional apathy (Atkins et al., 2021). Moreover, this study demonstrated a significant interaction between disease stage and subtype, in which manifest HD participants experienced similar levels of apathy severity across all subscales, whereas premanifest participants reported significantly less executive apathy relative to initiation apathy. The authors interpreted this to mean that the executive apathy dimension may develop at later stages of the disease, corroborating results from **Study 1**. In contrast to our HD sample, emotional apathy was reported in both premanifest and manifest individuals for both self- and observer-rated scales, but not at a clinically relevant level.

The lack of clinically significant differences in emotional apathy between patients and healthy controls poses more than one possibility. On the one hand, it may be true that this apathy dimension is not significantly represented in HD, as shown in the above studies and in this Doctoral Thesis. On the other hand, people with HD may simply lack awareness into their own emotional responses, blunted or otherwise, although this is not as relevant for informant-based scales.

In further congruence with our findings, another study again utilized the Dimensional Apathy Scale and reported that HD patients (in mild to moderate disease stages) selectively displayed lower cognitive/behavioral initiation and poorer goal-directed planning compared to healthy controls (Poletti et al., 2022). Interestingly, even from a qualitative perspective, individuals with HD describe their lived experience of apathy along themes that correspond with dimensions of cognitive generation (i.e. difficulty

identifying goals) and reduced initiation (Atkins et al., 2022). Fifty percent of these participants had clinically relevant apathy as quantified by the full-length LARS.

Taken together, the above studies examining apathy in HD substantiate the existence of apathy dimensions in HD. Of these, cognitive apathy and auto-activation deficit seem to bear certain predominance. However, whether the emotional, cognitive, or behavioral dimensions arise earliest in the disease process (i.e., in premanifest individuals), or in what combination, is still a subject of debate.

8.3.2 Apathy Profiles in Other Neurodegenerative Disorders

The prominent cognitive and self-initiation profile of apathy elicited in HD in **Study 1** and **Study 3** does not necessarily translate to other neurodegenerative disorders. For example, when considering apathy profiles in HD compared with Parkinson's disease and amyotrophic lateral sclerosis, those with HD demonstrated significantly greater levels of apathy in 1) the executive domain compared to the other two diseases and 2) in the initiative domain compared to amyotrophic lateral sclerosis only (Poletti et al., 2022).

When delving deeper into the dimensions of apathy in Parkinson's disease, results demonstrate a profile similar to HD, although perhaps with less overall prevalence. In particular, one study using the clinician version of the Apathy Evaluation Scale reported that apathy was present in 42.5% of Parkinson's patients, compared to 51.7% of HD patients (Sousa et al., 2017). Across disease stages, both Parkinson's and HD patients manifested the most severe scores in cognitive apathy, followed by auto-activation deficit, then emotional apathy. Similar to Poletti et al., 2022, a significant difference between the two disease cohorts was only found in the cognitive apathy dimension (i.e., higher scores in HD compared to PD), although, as mentioned previously, cognitive apathy remained the most severe relative to the other two dimensions in both diseases (Sousa et al., 2017).

Earlier studies employing the LARS in Parkinson's disease generally follow this trend, reporting greater dysfunction in action initiation and intellectual curiosity domains (Drijgers et al., 2010; Dujardin et al., 2007, 2014). Still, approximately 52% of apathetic Parkinson's disease patients satisfied the emotional apathy domain according to the Robert et al. (2009) diagnostic criteria (Drijgers et al., 2010). In another study, emotional

apathy was found to be significantly higher compared to healthy controls only in certain Parkinson's patient subgroups, namely more severe phenotypes (Dujardin et al., 2007). One study using the Dimensional Apathy Scale underscored that patients self-reported higher levels of both executive and initiation apathy than controls, but not emotional apathy (Radakovic et al., 2018). Another evidenced significantly higher apathy in initiation and emotional domains (Santangelo, D'Iorio, et al., 2017). Overall, while there appears to be some variability between studies, the general consensus points to elevated apathy in auto-activation and cognitive domains in Parkinson's disease, with emotional apathy being elevated to a lesser extent. Lastly, and similar to the dimension reduction analysis of **Study 3**, executive apathy in Parkinson's has been shown to associate with activities of daily living and quality of life (D'Iorio et al., 2017; Radakovic et al., 2018).

In amyotrophic lateral sclerosis, apathy appears to be represented by a profile of solely initiation apathy (Radakovic et al., 2016; Santangelo, Siciliano, et al., 2017). Meanwhile, another recent study found that a subset of amyotrophic lateral sclerosis individuals with lower empathy portrayed higher levels of emotional apathy only (Radakovic, Gray, et al., 2020). When considering the recent work by Poletti et al. (2022) directly comparing apathy in HD and amyotrophic lateral sclerosis, the apathy profile in HD is the most profound in terms of the severity of global apathy and discrete apathy dimensions (Poletti et al., 2022). Collectively, these studies support the notion that each disease may display a unique apathy profile.

In two related studies juxtaposing apathy profiles in Alzheimer's disease and behavioral-variant frontotemporal dementia, all three apathy dimensions (i.e., cognitive, affective, behavioral) were higher in behavioral-variant frontotemporal dementia (Kumfor et al., 2018), whereas executive apathy was greater in Alzheimer's disease only at later stages of the disease (Wei et al., 2019). Within-group analyses revealed that frontotemporal dementia participants exhibited more affective and cognitive apathy than behavioral apathy, while Alzheimer's participants showed highest cognitive apathy, followed by affective apathy and lastly behavioral apathy (Kumfor et al., 2018). Nonetheless, all three subdimensions of apathy were elevated in both patient groups compared to controls (Wei et al., 2019). These results corroborated past work in the two neurodegenerative diseases (Quaranta et al., 2012). Using the Neuropsychiatric Inventory, largely considered a

unidimensional measure of apathy, individuals with behavioral-variant frontotemporal dementia expressed lack of initiation, reduced emotional output, and reduced interest toward friends and family members more frequently than those with Alzheimer's (Quaranta et al., 2012).

Another study employing the LARS substantiated that participants with behavioral-variant frontotemporal dementia exemplified greater disturbances in emotional apathy compared to Alzheimer's disease (Fernandez-Matarrubia et al., 2018). In a study of two dementia syndromes (Alzheimer's disease and Progressive Supranuclear Palsy), both diseases demonstrated greater apathy in the initiative domain when compared to emotional blunting (Stanton et al., 2013). Interestingly, auto-activation deficit and cognitive apathy have been shown to be largely prevalent across Parkinson's disease, Alzheimer's disease, mixed dementia, and mild cognitive impairment, with emotional apathy only being predominant in schizophrenia, along with cognitive apathy (Mulin et al., 2011; Yazbek et al., 2014). To the author's knowledge, other than the work of Poletti and colleagues (Poletti et al., 2022), no study has yet compared the apathy profiles of these neurodegenerative diseases to HD.

Overall, these studies illuminate disparities in the severity and frequency of cognitive, emotional, and behavioral dimensions across different patient populations. While there is some overlap, the current evidence points to an etiology and thus underlying neurological basis of apathy profiles that are likely heterogeneous between diseases. This underscores the need for the continued study of apathy dimensions, including operationalization of the definition of apathy dimensions and delineation of the specific mechanisms at play. These concepts will be touched on in the following sections.

8.3.3 Integrating Frameworks for Multidimensional Apathy

As alluded to in the introduction, alternative frameworks for apathy beyond the classic three-dimensional model have emerged in recent years which follow a neurocognitive perspective. These conceptualizations define apathy as a deficit rooted in effort-based (i.e., cost-benefit) decision-making. One model focuses on three systems of normal motivated behavior, relating them according to brain bases (Le Heron et al., 2019). Specifically, these include the valuation system (evaluating the putative reward and effort

of a given future behavior), the motor system (producing the behavioral action), and the mediating system integrating the two. Outcome feedback and learning can occur within both habitual and goal-directed systems, with the former being easy to execute but inflexible (predominantly controlled by the striatum), and the latter being flexible and cost-intensive (predominantly controlled by the cortex, such as the ACC) (Le Heron et al., 2019). As such, novel stimuli tend to require higher-level cognitive functions.

In such a way, this effort-based decision-making model could conceivably fall into the triadic structure composed by (R. Levy & Dubois, 2006), with reward-valuation deficits resulting in emotional apathy, motor deficits leading to auto-activation deficit (including behavioral self-initiation apathy), and mediating deficits producing cognitive apathy (if higher-level executive functions are demanded). Neuroscientific research in this area currently focuses on distinguishing the neural and cognitive mechanisms underlying the following phases: representation of value, integration of effort costs, option generation, decision-making leading to option selection, reward anticipation ('wanting'/incentive salience), action and effort required to obtain the reward, reward consumption ('liking'), and, finally, reward learning/prediction error (Husain & Roiser, 2018).

Recent work in HD has demonstrated that both premanifest and manifest individuals evince greater aversion to cognitive effort, but not motor effort (Atkins et al., 2020, 2024). This is true even after controlling for task performance in manifest patients (Atkins et al., 2024). It should be noted that there was no association between aversion to effort and apathy, which the authors tentatively attributed to insufficient power. Meanwhile, in a combined premanifest and manifest HD cohort, another study revealed impaired instrumental learning and insensitivity to loss, but no alterations in reward-related effort (McLauchlan et al., 2019). Collectively, this work substantiates the notion that motivation is underpinned by various underlying mechanisms. Hence, different motivational deficits may be represented by dysfunction of unique processes of effort-based decision-making (e.g., effort valuation, sensitivity to loss), resulting in multiple dimensions of apathy.

When focusing specifically on higher-order cognitive functions, another neurocognitive conceptualization composed by Radakovic & Abrahams (2018) is closely related to the above model (Le Heron et al., 2019), but incorporates Stuss's scheme of executive functions (Stuss, 2011; Stuss & Alexander, 2007). Denominated the Dimensional Apathy

Framework, this model begins with initiation, followed by executive and later emotional processes (Radakovic & Abrahams, 2018). First, initiation apathy is attributed to deficits in energization or self-generation of thoughts, leading to decreased spontaneity or productivity. Second, executive apathy entails impaired executive functions involved in planning, organization, attention, and managing goals. This leads to inability to carry out task setting and monitoring of outcomes. Third, emotional apathy is characterized by reduced behavioral/emotional self-regulation, resulting in affective flattening, indifference, emotional blunting, and impairments in emotional integration. In theory, this model could be extended to include action initiation as the final step for self-generation of movement to complete tasks, a process which may also be disrupted in initiation apathy. As such, these domains also plausibly fit within the triadic structure of R. Levy & Dubois (2006), with auto-activation encompassing both the initiation of thoughts (energization step) and the final motor activation step (R. Levy & Dubois, 2006).

Lastly, it is important to note that there is still debate about the existence of an isolated cognitive apathy domain, as well as a separate social apathy domain (Dickson & Husain, 2022; D. S. Miller et al., 2021). The case for maintenance of cognitive (executive) apathy as a separate domain, but not social apathy, is made in **Box 8.1**. These findings are in line with the principal component analysis of **Study 3** of this Doctoral Thesis, in which social apathy did not load cleanly on any one domain.

Box 8.1. The Debate: Do Cognitive and Social Apathy Exist?

In a recent viewpoint, Dickson & Husain argue that, while there is evidence for behavioral and emotional domains of apathy, the **cognitive apathy** domain should be reconsidered (Dickson & Husain, 2022). In partial agreement with the authors, it is possible that one may have executive dysfunction without meeting diagnostic criteria for apathy (Cammisuli & Crow, 2018; Corbo & Casagrande, 2022), as well as apathy without executive dysfunction (Gonçalves et al., 2020). However, this Doctoral Thesis contends that this statement is not incompatible with the three-dimensional structure of apathy proposed by R. Levy & Dubois (R. Levy & Dubois, 2006).

Indeed, it may well be that distinct aspects of cognition underlie each of the three domains. For example, auto-activation deficit or initiation apathy encompasses self-generation of thoughts (i.e., cognition) as well as actions (i.e., behavior/motor function). For instance, initiation apathy has been associated with deficits in internal response generation and energization through a verbal fluency task (Radakovic, Stephenson, et al., 2017). Meanwhile, emotional apathy may embody components of emotional self-regulation as well as reward learning and prediction error, which are arguably cognitive components. Supporting this, elements of social cognition, such as emotion recognition and theory of mind, have been linked to apathy in neurocognitive disorders (Narme et al., 2013; Santangelo et al., 2012), including HD (Osborne-Crowley et al., 2019). Moreover, emotion perception deficits were specifically related with affective apathy in acquired brain injury (Njomboro & Deb, 2014). What R. Levy & Dubois (2006) outlined as cognitive apathy, then, may perhaps be best defined as apathy following the disruption of basic executive functions. As reiterated by Radakovic & Abrahams (2018), executive functions play a role in task setting and monitoring, involving processes such as planning, organization, attention, and managing goals (Radakovic & Abrahams, 2018).

Following the current and historical diagnostic criteria for apathy (D. S. Miller et al., 2021; P. H. Robert et al., 2009; Starkstein, 2000), where two out of three dimensions are required for apathy diagnosis (see *§ 1.3.1 Diagnostic Criteria of Apathy* for a review), it is possible that an individual is diagnosed with apathy through manifestation of the emotional and behavioral dimensions, without requiring disruption in the cognitive (i.e., executive) dimension. In summary, demonstrating executive dysfunction is not sufficient or necessary to be diagnosed with apathy. At the same time, what was formerly named cognitive apathy may be best defined as executive apathy, whereas distinct aspects of cognition underlie behavioral and emotional apathy.

In a similar way, **social apathy** may permeate through each of the three aforementioned apathy dimensions. This can be seen through the examples given for all three apathy dimensions in the Robert et al. (2018) diagnostic criteria (P. H. Robert et al., 2018), which included a separate social apathy dimension, as well as the questions pertaining to the social motivation domain of the Apathy Motivation Index (Ang et al., 2017). Utilizing the three-dimensional apathy framework, a patient could demonstrate social apathy through reduced social initiative or initiation of conversation (i.e., auto-activation deficit or initiation apathy; "I don't start conversations without being prompted"), emotional indifference to social activities (i.e., emotional apathy; "I don't enjoy doing things with people I have just met"), or decreased capacity to generate and monitor a plan (e.g., cognitive apathy; "I don't suggest activities for my friends and me to do").

Recent evidence has revealed associations between apathy and social cognitive deficits, such as emotional recognition in neurologic conditions with fronto-striatal pathology (Drapier et al., 2006; Hendel et al., 2023; Martínez-Corral et al., 2010; Radakovic, Stephenson, et al., 2017; G. Robert et al., 2014). A social subcomponent has also been revealed within the emotional apathy dimension (M'Barek et al., 2020). In another study across five forms of dementia, social reward learning significantly predicted scores in the emotional apathy dimension (Wong et al., 2023). There is also evidence that self-initiation and social domains of empathy relate with motivation to exert effort to benefit ourselves or other people, possibly substantiating a shared initiation component (Lockwood et al., 2017). Moreover, social blunting has been shown to be attributable to social cognitive deficits in HD (Bora et al., 2016; Kempnich et al., 2018; Philpott et al., 2016). In conclusion, it is plausible that components of both social apathy and cognition may be disseminated through all three apathy dimensions. However, while there is evidence of a distinct executive apathy dimension, an independent component of social apathy has not yet been demonstrated, as recent apathy instruments and diagnostic criteria support (D. S. Miller et al., 2021; Radakovic & Abrahams, 2018).

Ultimately, apathy may arise due to dysfunction at any step along the processes outlined above. **Figure 8.1** illustrates how these frameworks may conceptually be categorized according to the three-dimensional structure of apathy. This is acknowledged as a high-level view of the complex neurocognitive mechanisms underlying a psychiatric pathology. Nonetheless, identification of the unifying aspects of these frameworks serves as a crucial step to operationalize the clinical manifestations of distinct apathy dimensions, each of

which are represented by its underlying mechanism(s). In turn, this promotes the ensuing inception of clinical trials for therapeutics that target those dimensions that are most affected. In this way, research can take one step closer to developing personalized medicine for the unique apathy profile that an individual manifests, therefore translating the conceptual and neurobiological findings to clinical practice.

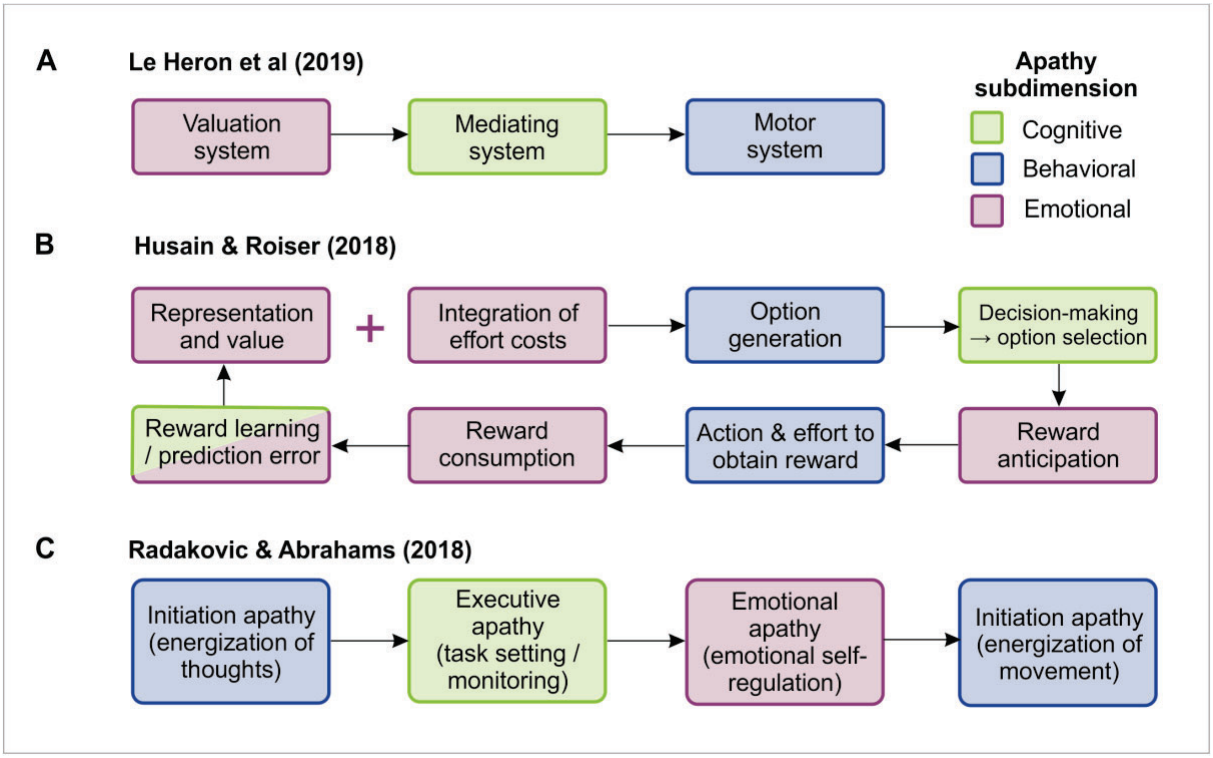


Figure 8.1. Apathy subdimensions may arise from disruptions along inter-connected processes of goal-directed behavior. Schematics of neurocognitive frameworks for goal-directed behavior as described by **(A)** Le Heron et al. (2019), **(B)** Husain & Roiser (2018), and **(C)** Radakovic & Abrahams (2018). Proposed apathy dimensions that may affect these processes are color-coded for cognitive (green), behavioral (blue), and emotional (mauve/purple) dimensions.

8.4 Progress in the Operationalization of Apathy

As alluded to above, operationalization (i.e., the translation of abstract conceptual ideas into measurable observations) is an important step in the understanding of apathy both in research and clinical spheres (Cummings et al., 2015). To do so, it is crucial to study the psychometric and clinometric properties of various apathy scales. In light of recent evidence, including the findings of **Research Aim 1** (**Study 1** and **Study 3**), there is a dire need for studies comparing multiple scales that are capable of capturing apathy dimensions.

8.4.1 Psychometrics of the Short-Lille Apathy Rating Scale

At this time, the PBA-s apathy domain continues to be the most frequently used apathy assessment tool in HD (Abdollah Zadegan et al., 2023) and is currently recommended to assess apathy in HD clinical trials (Carlozzi et al., 2014). However, this scale is only capable of capturing the unidimensional construct of apathy. Meanwhile, the results of **Study 3** support the use of the LARS-s as a dimensional apathy instrument in HD. The LARS-s demonstrated construct validity, as presented via convergent validity with the PBA-s apathy domain and discriminant validity with depression. This has since been substantiated with the full-length LARS in a combined premanifest/manifest HD cohort (Hendel et al., 2021). In light of this, researchers and clinicians may consider replacing the PBA-s apathy domain with the LARS-s, which takes a similar amount of time to administer for those who screen positively for apathy (approximately 5 minutes), but is capable of capturing distinct apathy dimensions, unlike the PBA-s.

In this vein, recent recommendations for assessing apathy as a primary endpoint in clinical trials have suggested rapidly screening for apathy with a dichotomous question (yes/no), and then proceeding to more in-depth evaluation for those who screen positive (Lanctôt et al., 2021). Already, two randomized control trials in people with Parkinson's disease leveraged the LARS to assess apathy improvements as primary or secondary endpoints (Devos et al., 2014; Moreau et al., 2012). Both studies showed that the LARS was sensitive to change over the time course of the study. However, the majority of studies to date utilize the apathy item of the Neuropsychiatric Inventory, which does not comprehensively measure apathy along its distinct dimensions (Lanctôt et al., 2017). By identifying the dimensional apathy profile exhibited by a patient with a valid and reliable tool such as the LARS-s, we move one step closer to characterizing and thereby treating the burden of apathy through an individualized approach.

8.4.2 Apathy Tasks: Potential for Objective Measurement

At present, questionnaires are the most common instruments employed to quantify apathy, whether self-reported or in the presence of a knowledgeable informant or clinician (Clarke et al., 2011; Mestre et al., 2016; Radakovic et al., 2016). However, self-reported measures may underrepresent the severity of apathy due to the fact that many

individuals with neurocognitive disorders, including HD in particular, are prone to anosognosia and lack of self-awareness (Gunn et al., 2020; D. Isaacs et al., 2020; Rosen, 2011), especially at later disease stages (Chatterjee et al., 2005; Sitek et al., 2014) (but see Baake et al. (2018) and Mason & Barker (2015)). Even when rated by a clinician or caregiver, these metrics are inherently subjective (R. Levy, 2012; Sockeel et al., 2006). In addition, ongoing discussions question the ability of external observers to be able to appreciate internal states such as motivation and emotional blunting (R. Levy & Dubois, 2006; M. E. Strauss & Sperry, 2002). As a whole, this has spurred a search for other more objective measures to evaluate apathy.

Ambulatory actigraphy has been employed to monitor diurnal variations in locomotor activity and has already been related with apathy evaluation scores (U. Muller et al., 2006; Zeitzer et al., 2013), including all three individual apathy dimensions in one study (David et al., 2012). A similar concept has been implemented with life space using readily available GPS (Global Positioning System) technology, although results are difficult to distinguish from depression (Tung et al., 2014). Subsequently, a tablet-based Motivation Application (MoTap) was designed as a series of mini-games to assess clinical dimensions of apathy, namely attention and sensitivity to reward, emotional reactivity, and cognitive interests (P. H. Robert et al., 2019). The Interest game quantifies the number of categories and sub-categories of interest, and has been related with apathy based on Apathy Diagnostic Criteria (Manera et al., 2023; Zeghari et al., 2020). Additionally, communication-technology and information-technology modalities have also been employed, such as machine learning analysis of voice (König et al., 2019) and facial dynamics (Happy et al., 2019). Furthermore, eye tracking has uncovered that individuals with apathy show abnormally diminished attentional bias toward social-themed stimuli (Chau et al., 2016). However, many of the above approaches are limited when employed in movement disorders, where physical limitations may confound results.

In light of this, there has been a recent push to develop novel tasks that can quantify apathy, both in terms of behavioral manifestations as well as neurological correlates. One approach to evaluating apathy mechanistically has focused on self-initiated action (Kos et al., 2017). Adapting a functional MRI task originally devised in Hoffstaedter et al. (2013), these authors replicated activation in fronto-parieto-striatal regions known to be

involved in self-initiated movements; however, they failed to find a relationship with apathy in their sample of the healthy population (Kos et al., 2017). As a result, they hypothesized that other dimensions of apathy besides auto-activation may be at play in the healthy population, including reward-processing, effort-based decision-making, and outcome devaluation (Bonnelle et al., 2015, 2016; Chong et al., 2016; Luther et al., 2018). In otherwise healthy individuals with behavioral apathy as measured by the LARS, a computer game was designed to assess effort- and reward-based decision-making, including components of incentive, effort and reward evaluation, cost-benefit weighing, and anticipation or preparation of effort production (Bonnelle et al., 2015, 2016). Similar tasks assessing effort-based decision-making and sensitivity to reward and punishment have since been implemented in HD (Atkins et al., 2020, 2024; McLauchlan et al., 2019).

In a similar effort-related paradigm, one study devised a touchscreen-delivered progressive ratio task to identify the breakpoint, or the highest number of touchscreen responses evoked, before task disengagement (Heath et al., 2019). The breakpoint score correlated negatively with the Apathy Evaluation Scale score, in that higher apathy was related with a lower breakpoint (earlier disengagement), in a way that was independent of motor disturbances. The progressive ratio task was also applicable in transgenic mice, allowing advancements in translational medicine.

Meanwhile, Massimo et al. developed the Philadelphia Apathy Computerized Test, which utilizes reaction times while controlling for motor slowing to assess the three domains of apathy: initiation, planning, and motivation (Massimo et al., 2014). To our knowledge, this is the only apathy task that has the potential to disentangle distinct apathy dimensions. The three domains measured by this computerized test are in line with the three dimensions of the LARS-s quantified in **Study 1** and empirically dissociated by dimension reduction analysis in **Study 3**. In accordance with the apathy scales that captured executive and initiation dimensions of apathy Parkinson's disease (Drijgers et al., 2010; Dujardin et al., 2007, 2014; Radakovic et al., 2018), the Philadelphia Apathy Computerized Test similarly reflected specific initiation and planning deficits in this population (Fitts et al., 2016). All three domains have also been shown to be impaired in behavioral-variant frontotemporal dementia (Massimo et al., 2015), again corroborating results utilizing apathy scales. While this task has not yet been implemented in HD, the so-called

Persistence and Maze tasks testing sensitivity to negative outcomes and option generation/selection, respectively, have been found to predict PBA-s apathy scores across time (E. Hare et al., 2022), and could bear potential for evaluating distinct dimensions of apathy.

In closing, a number of objective and task-based measures of apathy have been developed in the last decade. Many of these initiatives have emerged in parallel with the work of this Doctoral Thesis. Future endeavors that aim to tease apart the mechanistic underpinnings of apathy in relation to apathy dimensions can now leverage these objective measures of apathy.

8.5 Neural Correlates of Apathy Dimensions

Recent reviews have pinpointed large-scale frontostriatal networks and, more recently, the frontoparietal network as underlying global apathy in neurological disorders (Kos et al., 2016; Lanctôt et al., 2017; Parrotta et al., 2024; Steffens et al., 2022; Yan et al., 2023). Specific regions within the frontostriatal networks seem to at least partially overlap across these disorders, and include the ACC, OFC, insula, ventral striatum, and dlPFC (Bonelli & Cummings, 2007; Steffens et al., 2022; Tekin & Cummings, 2002). Overall, the work of **Research Aim 2** (**Study 1**, **Study 2**, and especially **Study 3**) substantiate these findings. Collectively, these results highlighted a relationship between greater apathy scores and decreased connectivity in WM microstructure of frontostriatal circuits (**Study 1**), specific GMV atrophy in the integratory hub that is the MCC (**Study 2**), and reduced volume in GM nodes in large-scale frontostriatal and inferior-parietal networks encompassing cortical and subcortical regions (**Study 3**). This section will focus on the neural correlates of apathy dimensions. To date and to the author's knowledge, no other study has yet assessed the brain regions and networks involved in apathy dimensions in HD other than the work of the current Doctoral Thesis. As there is minimal existing data with which to compare these results, the Discussion is centered on the corresponding evidence of brain correlates of apathy dimensions in other neurodegenerative diseases. **For ease of interpretation, neural correlates in the literature that were similarly**

identified in this Doctoral Thesis for a given apathy dimension are underlined in the text.

At present, most work on the neural correlates of apathy dimensions in neurodegenerative disease is focused on dementia syndromes, including Alzheimer's disease and behavioral-variant frontotemporal dementia. Methodologically, these studies have utilized both dimensional scales, such as the LARS and Dimensional Apathy Scale (Radakovic & Abrahams, 2014; Sockeel et al., 2006), as well as objective measures of apathy dimensions, such as the Philadelphia Apathy Computerized Test (Massimo et al., 2014). Across these diseases, neuroimaging evidence has elucidated both common and divergent prefrontal and subcortical neural correlates associated with apathy dimensions, illustrating that distinct processes of goal-directed behavior may be somewhat dissociable on a neurobiological basis.

Across the literature, and as reviewed in earlier sections, apathy dimensions are defined with slightly varying terminology (see **Table 1.1** for review). The dimension of cognitive apathy is characterized as apathy resulting from deficits in executive functioning (e.g., planning) or loss of interest. Auto-activation deficit, meanwhile, is conceptually similar to initiation apathy, or behavioral/cognitive apathy when considering self-activation of behaviors and thoughts. Emotional apathy encompasses affective processing, motivation (ability to associate affective (positive or negative) signals with value when performing actions), and emotional blunting. While this will be specified below for each case, it is important to keep in mind that these studies may be capturing slightly differing albeit related concepts within a similar construct.

8.5.1 Cognitive Apathy

Across studies and neurodegenerative populations, cognitive apathy has been associated with large-scale regions involved in executive control of planning, self-initiated movements, and stimulus-reward contingencies. Utilizing exclusive masking in a combined Alzheimer's disease and frontotemporal dementia group, executive apathy was uniquely associated with decreased GM intensity in the left OFC, bilateral frontal pole, lateral temporal regions including the right middle temporal gyrus and temporal pole, as well as the left supramarginal and angular gyri (Wei et al., 2019). Using a similar approach

in a related population, exclusive masking revealed that cognitive apathy was uniquely associated with more dorsal prefrontal cortical regions, including the paracingulate gyrus, bilateral frontal operculum cortex and superior frontal gyrus (Kumfor et al., 2018). With inclusive masking to assess common regions across apathy subdimensions, cognitive apathy was associated with lower intensity in the left OFC and subcallosal regions, extending dorsally into the medial prefrontal cortex, ACC and superior frontal gyrus, as well as the inferior temporal gyrus and posterior cingulate cortex. The authors themselves state that the findings occurred in more medial areas than first expected (e.g., dmPFC vs. dlPFC). In an earlier functional imaging study employing SPECT for brain perfusion, the lack of interest score, as measured by the Apathy Inventory, was correlated with hypoperfusion in right middle orbitofrontal gyrus in Alzheimer's disease (Benoit et al., 2004), consistent with the abovementioned structural studies.

Many of these brain regions were elucidated in **Study 3** in the HD population. Specifically, cognitive apathy was associated with decreased GMV in nodes such as the OFC, inferior frontal operculum, angular gyrus, supramarginal gyrus, superior medial frontal gyrus and neighboring SMA, middle temporal lobe, and temporal pole. Decreased GMV and WM connectivity in these regions have similarly been implicated in apathy when measured as a unidimensional construct in HD (Delmaire et al., 2013; Martinez-Horta et al., 2018). Separating out specific apathy dimensions in future studies may highlight the specificity of these regions in cognitive apathy. Likewise, increased cognitive apathy was also associated with reduced GMV in the inferior parietal area, MCC, and insula in **Study 3**. Such regions have likewise been implicated in global apathy in neurological populations, as highlighted in recent reviews (Kos et al., 2016; Lanctôt et al., 2017; Parrotta et al., 2024; Steffens et al., 2022; Yan et al., 2023).

Lastly, in behavioral-variant frontotemporal dementia, a computerized test of apathy dimensions evinced that planning-related apathy (i.e., cognitive apathy) was related to GM atrophy in the dlPFC (BA 9) and OFC (BA 11) and reduced WM integrity in the superior longitudinal fasciculus, inferior frontal-occipital fasciculus, rostral frontal corona radiata, corpus callosum, and posterior thalamic radiations (Massimo et al., 2015). While we did not study these particular tracts in this Doctoral Thesis, **Study 3** did highlight reduced GMV in some of the regions connected by the disrupted WM tracts in the above study (e.g.,

thalamus). Reduced GMV in the thalamus has also been implicated in apathy in HD specifically (Baake, Coppen, et al., 2018), although apathy was measured as a unidimensional construct. Meanwhile, in the related **Study 1**, cognitive apathy was significantly related with reduced WM integrity in tracts connecting the regions implicated in the above studies, such as the dlPFC-cn as well as the FST linking the caudate nucleus to the preSMA/SMA (i.e., dmPFC). Collectively, these results emphasize that executive functions necessary for devising and managing goal-directed behavior may be compromised following damage to the dlPFC and associated WM tracts linking the dlPFC with other neural nodes.

Classically, the dlPFC is a region involved in executive functions, including planning, problem-solving, and rule-based behavior (Di et al., 2014; E. K. Miller & Cohen, 2001). This region has previously been related with apathy in behavioral-variant frontotemporal dementia (Massimo et al., 2009; Zamboni et al., 2008). Meanwhile, the SMA serves as an anatomical and functional relay between the primary motor cortex and basal ganglia, playing a role in motor planning and executive control of self-initiated movements, action monitoring, response inhibition, and action sequencing (Nachev et al., 2008). Decreased connectivity between the SMA and MCC has been associated with increased behavioral apathy (Bonnelle et al., 2016). Lastly, the OFC is typically associated with limbic functions and emotional processing (Kumfor et al., 2013). At the same time, it has been proposed that the OFC mediates these operations via executive control functions that process complex stimulus-reward contingencies (T. A. Hare et al., 2010; Ursu & Carter, 2005). For example, while the dlPFC collects salient information and then controls cognitive processes such as attention and working memory (Menon & Uddin, 2010), the ventromedial prefrontal cortex applies information from past behavioral outcomes to the current context on the basis of subjective feelings, and then formulates goals to make decisions on future actions (Weller et al., 2009). As such, damage to the OFC may result in distractibility and inability to engage in mental flexibility when carrying out goal-directed actions (Bechara, 2000; Wei et al., 2019).

8.5.2 Auto-Activation Deficit

Typically, auto-activation deficit, or the behavioral initiation domain, is linked with deficits in large-scale cortical and basal ganglia regions involved in movement initiation and the integration of motivation and effortful actions, including the MCC (denominated the dACC in some studies). Again utilizing exclusive masking in a combined Alzheimer's disease and frontotemporal dementia cohort, initiation apathy was uniquely associated with reduced GM intensity in the right medial prefrontal cortex, left frontal pole, OFC, the right paracingulate, and the anterior and posterior cingulate (Wei et al., 2019). This was partially replicated in a similar study that revealed a link between behavioral apathy and lower GM intensity in the frontal pole and right precentral gyrus (Kumfor et al., 2018).

In general, the precentral gyrus, cerebellum, and putamen constitute motor regions that are required to initiate movement. As Kumfor and colleagues (2018) interpret, damage to these lower-level regions may lead to a "basic inertia" or an inability to carry out behavioral self-activation, leading to the severely apathetic auto-activation deficit. This study also revealed a link between behavioral apathy and reduced GM intensity in the basal ganglia, including the left caudate extending to the nucleus accumbens as well as the cerebellum (Kumfor et al., 2018).

In Alzheimer's disease, lack of initiative score was negatively correlated with perfusion in right ACC (Benoit et al., 2004). In a follow-up functional MRI study, a combined domain of lack of initiative/interest was significantly related with perfusion in the right OFC (BA 11) and inferior temporal lobes (BA 20) (P. H. Robert et al., 2006). Meanwhile, the group with worse apathy in initiative/interest domains evidenced hypoperfusion in the right ACC (BA 32). Lastly, both Alzheimer's disease and Progressive Supranuclear Palsy patients with reduced initiative displayed atrophy of the subgenual ACC and ventrolateral OFC, including the rectus gyrus, as well as increased GMV in the right lingual gyrus and left cuneus (Stanton et al., 2013). In contrast to this last finding, **Study 3** demonstrated a negative relationship between GMV and auto-activation deficit, particularly with reduced GMV in the right lingual gyrus.

When leveraging an objective computerized task, reduced initiation was related to GM atrophy in the dACC in behavioral-variant frontotemporal dementia and reduced WM

connectivity in the right UF, cingulum, inferior longitudinal fasciculus, and corpus callosum (Massimo et al., 2015). Similar to **Study 1**, those with worse auto-activation deficit scores revealed reduced WM connectivity specifically in the right UF. This underscores the importance of WM bundles, and this tract specifically, in behavioral initiation in both behavioral-variant frontotemporal dementia and HD. Interestingly, the UF has been previously tied to goal-directed behavior (Kable & Glimcher, 2007) and apathy in particular (Hahn et al., 2013). The amygdala, which the UF dually connects to the anterior temporal lobe and the ventral prefrontal cortex, also plays a role in motivation (Jiang et al., 2014).

Regarding GM correlates, not all cortical regions underlying auto-activation deficit in HD aligned with the areas in other neurodegenerative disorders, as displayed above (Benoit et al., 2004; P. H. Robert et al., 2006; Wei et al., 2019). In **Study 3**, the regions that did not overlap with findings in other studies included the superior frontal gyrus, dlPFC, middle temporal lobe, and superior occipital gyrus. However, it is notable that auto-activation deficit was the only apathy dimension related with the basal ganglia in our study, similar to Kumfor and colleagues (Kumfor et al., 2018). Specifically, worse auto-activation deficit apathy scores were associated with decrease volume in the bilateral putamen in **Study 3**. Indeed, the putamen was the only striatal region that demonstrated an association with apathy, and only with the auto-activation deficit dimension.

Across studies, the ACC was related with reduced apathy of the initiation subtype. Reduced ACC activity has been previously associated with decreased spontaneous goal-directed behavior, impaired motor activity, and akinetic mutism (Devinsky et al., 1995). While **Study 3** did not elucidate a relationship between auto-activation deficit and GMV in the ACC in HD, global apathy was significantly related with decreased volume in this region. In addition, the MCC (denominated the dACC in some studies) and the ACC were associated with cognitive and emotional apathy in HD, respectively. Supporting this, Massimo et al. (2015) evidenced that the cingulate contributed to both initiation and motivation apathy (Massimo et al., 2015). In line with the broader literature (Le Heron et al., 2019), these findings may serve to support the role of the ACC as an integratory hub involved in multiple apathy dimensions, subsequently resulting in an association with global apathy severity. Indeed, **Study 2** demonstrated that atrophy specifically in the MCC

was associated with increasing apathy scores over time. Moreover, initial vulnerability in the MCC (i.e., lower baseline GMV in this region), was able to predict those individuals that would develop more severe and rapidly worsening apathy scores over time.

8.5.3 Emotional Apathy

Emotional apathy is largely associated with dysfunction in regions implicated in reward processing, explicit motivation, and assimilation of subjective feelings with goal-directed behavior. Utilizing exclusive masking in a combined Alzheimer's disease and frontotemporal dementia group, emotional apathy was uniquely associated with decreased GM intensity in the left amygdala, cerebellum bilaterally, as well as the ventral prefrontal cortex (i.e., left inferior frontal gyrus), and more posterior regions including the right postcentral gyrus, supramarginal gyrus, and the central opercular cortex (Wei et al., 2019). In a related population, exclusive masking revealed that affective apathy was uniquely associated with ventral prefrontal cortex regions including the left frontal pole, bilateral medial frontal cortex, and ACC (Kumfor et al., 2018). With inclusive masking to assess common regions, affective apathy was associated with lower GM intensity in the left temporal poles, extending to the bilateral OFC, subcallosal cortex, and bilateral insula.

When employing a computerized test of apathy dimensions in behavioral-variant frontotemporal dementia, poor motivation was related to GM atrophy in the OFC, ACC, and inferior frontal gyrus, as well as reduced WM integrity in the UF (Massimo et al., 2015). Interestingly, a functional (SPECT) study in Alzheimer's disease demonstrated an inverse relationship between the emotional blunting score and blood perfusion in left superior dlPFC (Benoit et al., 2004). In Alzheimer's disease and Progressive Supranuclear Palsy, the emotional blunting dimension was associated with atrophy in the left insula and increased GMV in the cerebellum, right middle occipital gyrus and left cuneus (Stanton et al., 2013).

Another study assessed the link between emotional apathy and reward learning with their accompanying neural correlates in dementia syndromes (Wong et al., 2023). They reported that both emotional apathy and social reward learning were jointly related with reduced GM intensity in fronto-striatal-insular regions. Higher levels of emotional apathy in isolation were associated with reduced GM intensity in the left insula extending to the

left OFC, bilateral supramarginal gyri, superior lateral occipital cortex, postcentral gyrus, and the right striatum (encompassing the caudate, putamen, and nucleus accumbens) as well as the cerebellum. Interestingly, **Study 3** likewise exemplified an inverse relationship between emotional apathy and GMV in the left insula, in addition to the left ACC, MCC, middle frontal lobe, and superior temporal lobe. However, the association with orbitofrontal GMV was only discovered in the cognitive dimension in the HD cohort. This may be attributed to reduced variability in the emotional apathy scores compared to those of the cognitive dimension.

These results are largely convergent with **Study 3**, in which emotional apathy as measured by the LARS-s was related with decreased GMV in the frontal medial cortex, insula, inferior temporal lobe, ACC as well as the MCC. However, emotional apathy was not related with the OFC in **Study 3**, nor with the UF (or any WM tract) in **Study 1**. This may be because there was relatively little emotional apathy expressed by our HD sample. Indeed, no significant differences were found between HD individuals and controls for this apathy dimension.

When considering these results in the context of the broader literature, lesion studies in individuals with subarachnoid hemorrhage portray the ventromedial PFC as involved in reward processing (Manohar & Husain, 2016). The ACC, meanwhile, has long been considered a nexus of various affective and sensory processes that play a role in the initiation of a goal-directed behavior (Devinsky et al., 1995). Both the structural and functional connectivity of the ACC extend to regions involved in emotion, autonomic function, and reward processing (Margulies et al., 2007; Sheline et al., 2009; Stevens, 2011). Next, the insula is believed to play a role in ascribing interoceptive sensory information to subjective feeling states, including emotional feeling (Gasquoine, 2014; Namkung et al., 2017). The insula also subserves explicit motivation, or the conscious desire to engage in behaviors by encoding incentive values of stimuli (Namkung et al., 2017). As such, it follows that damage to this reason may give rise to emotional blunting and difficulty integrating affective states with reward value.

8.5.4 Implications of Dimensional Apathy Networks

The above sections have considered the findings from **Research Aim 1** (apathy profiles) and **Research Aim 2** (neuroanatomical bases of these profiles) in the context of the wider literature. Bringing these together, it is clear that the apathy syndrome is a transdiagnostic construct, occurring across diseases. In addition, there is support for distinct neurobiological bases for specific apathy dimensions that are shared across these diseases. In other words, a specific apathy dimension may be represented by a common anatomical substrate, regardless of the primary disease process. At the same time, an individual may be more prone to expressing a specific apathy profile based on their underlying disease (e.g., more cognitive and auto-activation apathy in HD, more emotional apathy in behavioral-variant frontotemporal dementia).

Overall, the neuroanatomical findings discussed above largely fall in line with the three-dimensional model of apathy and its underlying prefrontal cortex-basal ganglia circuits described by R. Levy & Dubois (R. Levy & Dubois, 2006). In addition, **Study 2** of **Research Aim 2** revealed that atrophy or initial vulnerability in a specific brain region (i.e., the right MCC), may serve to predict apathy prognosis in HD. This opens a door to the initiation of targeted treatments during an optimal window, as well as facilitating enrollment of individuals with similar disease profiles into clinical trials.

Already, existent diagnostic criteria (D. S. Miller et al., 2021) and dimensional apathy scales with sufficient brevity for clinical practice such as the LARS-s allow the translation of diagnosing specific apathy dimensions in clinic. Doing so would promote the development of more individualized pharmacological management. For example, cholinesterase inhibitors or cholinergic precursors (which increase acetylcholine levels) have been shown to improve cognitive performance and thus may be preferred in the treatment of cognitive apathy, while methylphenidate (which increases levels of catecholamines) or dopaminergic agonists may be reserved for behavioral aspects of apathy in HD, such as auto-activation deficit (Nobis & Husain, 2018). Meanwhile, reward sensitivity is putatively involved in emotional apathy. As such, dopaminergic agents may ameliorate both auto-activation deficit as well as emotional apathy (Padala et al., 2007). Already, dopamine has been shown to salvage reward sensitivity in a case of apathy resulting from bilateral lesions to portions of the globus pallidus connecting to the OFC

and ventromedial prefrontal cortex (Adam et al., 2013), although specific apathy dimensions were not assessed.

When considering psychosocial interventions, cognitive apathy may benefit from reducing distractions and restructuring complex activities into smaller goals that require less planning and task management. Occupational therapies aimed to augment executive functions such as verbal planning, memory, and problem-solving has also been shown to be beneficial in HD (Cruickshank et al., 2015). Meanwhile, emotional apathy may be targeted through initiatives that promote rewarding outcomes and the social environment, such as increased social stimulation and effective communication (Wei et al., 2019).

8.6 Longitudinal Psychiatric Profiles in Huntington's Disease

At this time, it is widely recognized that neuropsychiatric syndromes exemplify highly variable progression over time. This is especially true in the neurodegenerative population (Cummings et al., 2024). In HD specifically, there remains unexplained variability in both the type and timing of psychiatric evolution. Other than apathy (Schobel et al., 2017), this does not consistently align with the progression of motor and cognitive symptoms (Duff et al., 2007; Epping et al., 2016; Ravina et al., 2008). Only recently have studies begun to tap into patient stratification based on longitudinal disease trajectories, some using machine learning approaches, including unsupervised clustering (Ko et al., 2023; Koval et al., 2022; Mohan et al., 2022; Raschka et al., 2024). Even so, and as will be reviewed below, many of these models omit the contribution of psychiatric disturbances in their initial patient stratification.

The findings of **Research Aim 3** thus sought to address this gap in knowledge pertaining to individual profiles of psychiatric evolution in HD. In doing so, this work sheds light on the severity and development of apathy in HD in the context of cognitive functioning and other psychiatric features. First, **Study 2** revealed that changes in apathy, but not depression or executive dysfunction, was related to atrophy in the right MCC. The MCC is an integratory hub of motivation (i.e., effort-based response-selection) and execution (Allman et al., 2006; Mega & Cummings, 1994; Theleritis et al., 2014). This is especially

pertinent when action selection is directed by reward anticipation and reinforcement for effortful actions (Massimo et al., 2009; Rushworth et al., 2007; Siegel et al., 2014). Interestingly, initial vulnerability (i.e., smaller baseline GMV, controlling for head size) in the MCC could predict the overall severity and rate of progression of both apathy and executive dysfunction over time, but not depression. Meanwhile, executive dysfunction, but not depression, was capable of predicting longitudinal apathy scores.

Next, **Study 4** harnessed a novel unsupervised clustering algorithm to stratify HD individuals into subgroups based on their longitudinal psychiatric disease trajectory. This is approach is unique in that it accounts for variations in dynamics of disease progression through non-linear alignment of temporal sequences. Across the HD sample, two main psychiatric signatures were revealed: one defined by increasing irritability (together with a rise in overall psychiatric disturbances and no depression) and the other by rise-and-fall depression (coupled with stable overall psychiatric disturbances and no irritability). Apathy and perseveration/obsessive-compulsive behaviors increased in both patient subgroups over time with clinically significant severity.

The ensuing subsections will review the findings of this Doctoral Thesis as they relate with the extant literature of psychiatric trajectories in HD. In particular, the discussion will focus on the longitudinal interrelation of apathy with executive functions and relevant psychiatric features, such as depression and dysexecutive behaviors (i.e., perseveration/obsessive-compulsive behaviors).

8.6.1 Apathy, Depression, and Executive Functions

The temporal profiles of apathy and its relationship with other relevant psychiatric features in HD revealed by **Research Aim 3** (**Study 2** and **4**) is corroborated by past literature. To start, a longitudinal study in a cohort of combined premanifest and manifest HD patients found that persistent apathy was exhibited by the majority (58.8%) of patients, meaning that apathy remitted in the minority (41.2%) of the cohort (Reedeker et al., 2011). This study was one of the first to consider clinical differences in apathy profiles in HD. Interestingly, of all individuals with apathy at baseline, those who later developed persistent apathy demonstrated a lower initial TFC score and impaired baseline executive functions, including processing speed (Symbol Digit Modalities Test)

and attention (Stroop Word Test). Similar to the results of **Study 2**, executive functioning (i.e., the Symbol Digit Modalities Test of psychomotor speed) was the only predictor of persistent apathy, although this did not reach statistical significance (Reedeker et al., 2011). Lastly, when considering depression in persistent vs. remitting apathetic groups, depression was found to be more (although not significantly) prevalent at baseline in the former than the latter (25% vs. 21.4%), which decreased at follow-up in both groups (20% vs. 0%).

In a recent five-year longitudinal study of apathy and depression in manifest HD (Connors et al., 2023), the overall severity and prevalence of apathy increased over time, as substantiated throughout this Doctoral Thesis. Like in **Study 4**, this was contrary to depression, whose prevalence remained the same over the course of the study, with a very slight decrease in depression severity over subsequent visits (Connors et al., 2023). At each point in time, apathy, but not depression, was related with lower scores in measures of global cognition, psychomotor speed, verbal fluency, and inhibitory control, while depression was only associated with worse verbal fluency. In this study, however, the longitudinal trajectories of the sample were analyzed as a collective group, without elucidating potential inter-individual differences or disease profiles. While rates of remission for psychiatric disturbances are not presented, approximately 60.5% and 74.6% of those with apathy at the earlier visit still had apathy in the following year. These rates were similar for depression. Both depression and apathy were associated with worse overall neuropsychiatric symptoms. However, only depression was associated with suicidal ideation.

Another five-year longitudinal study substantiated that both anxiety and depression decreased over time in early-moderate manifest HD (Ruiz-Idiago et al., 2023). These findings are similar to **Study 4**, which presented a rise-and-fall pattern of mood symptoms, as well as the decrease in depression discussed above (Connors et al., 2023). This could indicate the effectiveness of antidepressants in treating mood disturbances (Soliveri et al., 2022), in contrast to the relative ineffectiveness of treatments for many other psychiatric features, such as apathy (Cummings et al., 2024).

Contrary to the results of **Study 2**, depression scores (but not general cognitive impairment, as measured by the Montreal Cognitive Assessment) predicted apathy in a

mixed premanifest and manifest HD cohort (Hendel et al., 2021). It is important to note, however, that this study was cross-sectional, and so was unable to truly assess causation at a future point in time. Lastly, in comparison to **Study 1** and **Study 3**, the LARS global apathy score correlated with the PBA-s apathy score. However, only 14.6% of the sample demonstrated clinically relevant apathy when measured by the PBA-s, compared to 28% with the LARS (Hendel et al., 2021).

Of note, the above studies, including **Study 2** and **Study 4**, did not assess apathy dimensions. Looking to Alzheimer's disease, one study found that dimensional apathy scores as recorded in an apathy diary by caregivers corresponded with deficits in specific tasks (Perri et al., 2018). In particular, cognitive apathy scores were predicted by performance in a test of executive function (i.e., Modified Card Sorting Test) and emotional-affective apathy scores by performance on a task of emotion-attribution. Interestingly, auto-activation apathy was predicted by performance on both the executive and emotion-attribution tasks, underlining the notion that this dimension may manifest as the most severe apathy type.

Overall, there is a need for continued study of apathy using dimensional apathy scales in HD. Preferably, these studies may assess apathy with dimensional scales or diaries in comparison with standardized diagnostic criteria for assessment of the presence or absence of clinically relevant apathy. Lastly, it is crucial to continue to investigate the development of apathy dimensions over time to comment on cause and effects.

8.6.2 Apathy in Relation to Other Psychiatric Disturbances

As a whole, this Doctoral Thesis revealed that apathy increased over time with clinically significant severity. In **Study 4**, there was a longitudinal increase in apathy and perseveration/obsessive-compulsive behaviors in both psychiatric signatures. First considering cross-sectional evidence, a recent study characterized mental health symptoms in six disease stages of HD (i.e., premanifest and manifest Stages 1-5) compared to genotype-negative family members (Gunn et al., 2023). Mid-late manifest HD (i.e., Stages 2-5) demonstrated significantly higher apathy, obsessive-compulsive behaviors, and (from Stage 3-5) disorientation when compared to premanifest individuals or genotype-negative controls (Gunn et al., 2023). There were no significant differences

found in the remaining eight psychiatric indices (depression, suicidal ideation, anxiety, irritability, aggression, perseveration, paranoia, and hallucinations). The expression of the eight other psychiatric indices underscores previous findings that psychological distress is impactful in the lives of both carriers and noncarriers across HD-affected families (Achenbach & Saft, 2021; Maltby et al., 2021). Meanwhile, the heightened levels of apathy and obsessive-compulsive behaviors in HD are in line with **Study 4**.

Similarly, obsessive-compulsive behaviors have previously been related to HD progression and disease duration (Anderson et al., 2010). One study illustrated that early manifest HD patients in both fast and slow cognitive progression subgroups demonstrated increases in apathy and perseveration over time, while the fast progression group additionally exhibited increasing obsessive-compulsive and disoriented behaviors (Martinez-Horta et al., 2023). In another study, only apathy, perseveration, and psychotic symptoms were associated with TFC, a proxy of disease progression, while obsessions/compulsions, depression, anxiety, suicidality, irritability, and aggressiveness were not (Ruiz-Idiago et al., 2017). The lack of association between functioning and obsessions/compulsions, in contrast to perseveration, may be explained by the fact that patients are aware of the presence of their dysfunction with regards to the former, but not the latter (Oosterloo et al., 2019). Despite the fact that obsessive-compulsiveness, perseveration, and apathy increase along the time course of the disease, as shown in **Study 4**, psychiatric disturbances with preserved awareness (e.g., obsessive-compulsive behaviors) may not affect day-to-day functioning to an extreme degree (e.g., maintained ability to perform daily hygiene or pay bills) or to the same degree as those associated with anosognosia (e.g., apathy, perseveration). In support of this, a five-year longitudinal study in early-moderate manifest HD substantiated that, of all neuropsychiatric features, apathy and perseverative behavior demonstrated the strongest relationship with TFC (Ruiz-Idiago et al., 2023).

Of all neuropsychiatric signs in HD, only irritability was predicted by motor and cognitive progression over time in the study by Ruiz-Idiago and colleagues (Ruiz-Idiago et al., 2023). This has been exemplified in other studies (Craufurd et al., 2001; Nimmagadda et al., 2011; Thompson et al., 2012). However, other research evidences that most psychiatric features of HD (e.g., mood disturbances like anxiety and depression,

irritability/anger, and psychosis) are unassociated or only weakly associated with disease progression (Paulsen et al., 2001; van Duijn et al., 2013; Zappacosta et al., 1996). This further exemplifies the possibility of psychiatric profiles in HD, in which irritability may increase along the course of the disease in a selective group of patients, rather than across the whole cohort. One retrospective study that began to tap into risk factors found that the mean age of onset of irritability in relation to motor onset depended on CAG repeat length, with irritability tending to precede motor onset at shorter repeat lengths (40-43 CAG repeat expansions) and follow motor onset at longer repeat lengths (44-53 CAG repeat expansions) (McAllister et al., 2021). However, this analysis focused on the presence/absence of symptoms, meaning individual differences in the severity of irritability were not assessed.

In the first cluster in **Study 4** (increasing irritability in the absence of depression), the overlap of apathy with irritability in HD can be explained by the fact that both are propounded to involve fronto-striatal circuits (Abdollah Zadegan et al., 2023; Bouwens et al., 2015). However, the lack of association between apathy and cognitive dysfunction in Ruiz-Idiago et al. (Ruiz-Idiago et al., 2023) is surprising in the context of past literature that evinces a strong relationship between the two (Andrews et al., 2020; D'Iorio et al., 2017; Montoya-Murillo et al., 2019; van Reekum et al., 2005) and as highlighted in the previous section. On the other hand, the putative association between apathy and motor symptoms has been less consistent in the literature (Hendel et al., 2021; McAllister et al., 2021; Reedeker et al., 2010, 2011; Schobel et al., 2017; van Duijn, 2010). This includes **Study 1**, which did not show a relationship between apathy and motor symptoms in HD.

The study by Ruiz-Idiago and colleagues (2023) puts forth important longitudinal evidence of the interrelation of neuropsychiatric signs with clinical variables in manifest HD (Ruiz-Idiago et al., 2023). Nonetheless, it is important to note that the study is limited in that it only considered binary data (i.e., presence or absence) of psychiatric signs in their mixed models, with psychiatric scores based on severity alone (i.e., not considering frequency). Moreover, while the study presents discourse on possible disease profiles in HD, the authors did not perform analyses that permit the evaluation of subgroups or the severity and progression of psychiatric signs along a continuum, and therefore were unable to interpret individual differences or possible clusters within this cohort.

8.6.3 A Promising Perspective: Interrelating Psychiatric Features Through Disease Profiles

Recent work centering on disease profiles in HD substantiates that the relationship between symptom dimensions may depend on to which cluster they belong. In one study, parkinsonism-dominant individuals experienced more severe neuropsychiatric disorders (depression, apathy, obsessive-compulsive behaviors, and psychosis) independent of age of motor onset, motor duration/severity, CAG repeat expansion, and medication use (Julayanont et al., 2020). On the contrary, patients in the chorea-dominant group experienced less apathy and depression. Effectively, by highlighting a differential association between specific motor symptoms and neuropsychiatric development, this work forms part of an emerging body of literature that examines individual differences in HD gene-expansion individuals. In this way, this study underlines the value in analyzing individual differences to better understand disease progression, and in turn, optimize informed prognosis and treatment options for patients.

Showcasing state-of-the-art machine learning methods, two recent papers executed unsupervised clustering of longitudinal disease trajectories in HD. These methods closely mirror the clustering methodology presented in **Study 4** and Giannoula et al. (2024) by accounting for variations in the dynamics of disease progression (Giannoula et al., 2024). In one study in manifest HD, clustering was carried out using the UHDRS-TMS, Symbol Digit Modalities Test, and apathy as *a priori* outcomes to jointly determine clusters based on their longitudinal trajectories (Ko et al., 2023). This approach identified three clusters following rapidly progressive, moderately progressive, or slowly progressive trajectories. In the rapid progressors, apathy, irritability, and psychosis were more common than in the other two clusters at the enrollment visit. This cluster also possessed the longest CAG repeat length and CAP. Later, features considered predictive of disease trajectories were examined. At enrollment, CAP score, Body Mass Index, and age was predictive of rapid progression. Meanwhile, of psychiatric signs, only apathy history was predictive of the progression profile (Ko et al., 2023). In an earlier study in manifest HD, apathy was similarly found to be the only psychiatric sign to predict composite UHDRS scores and TFC (Ghazaleh et al., 2021).

Another study in manifest HD individuals identified two cohorts defined by stably progressive and dramatically more progressive disease trajectories (Raschka et al., 2024). The features (i.e., clinical variables) used during modeling and clustering consisted of the UHDRS-TMS, Symbol Digit Modalities Test, and the total Mini-Mental State Examination score. Clusters differed in the progression of all three scores as well as the baseline value of the Symbol Digit Modalities Test. Next, a novel classifier model was trained to predict the disease progressive subtype of a patient based on a wider range of baseline clinical data. The classifier was then evaluated for which features contributed most to the prediction, similar conceptually to the weight metric in **Study 4**. This is crucial for the clinical understanding of these profiles. The classifier found that, in addition to cognitive scores, CAG repeats, and motor scores, observable apathy and a history of perseveration/obsessive-compulsive behaviors were among the top most important features in the classifier for both fast and slow progressors (Raschka et al., 2024). Interestingly, while apathy and perseveration/obsessive-compulsive behaviors contributed to the prediction of both subgroups, they had a higher tendency to predict slow progressors. The slowly progressing patients constituted the majority of patients in the sample (94.5% of eligible manifest patients in initial clustering and 91.7% on validation). In turn, this emphasizes that apathy and perseveration/obsessive-compulsive behaviors are critical psychiatric components in a large percentage of HD patients, as was demonstrated in **Study 4**.

Importantly, as noted above, this classifier was trained using only motor (UHDRS-TMS) and cognitive (Symbol Digit Modalities Test and Mini-Mental State Examination) data. The authors themselves state that psychiatric scores are underrepresented in their study and warrant future research (Raschka et al., 2024). Other clustering algorithms have been applied, although they also did not take psychiatric features into account in clustering (Martinez-Horta et al., 2023; Mohan et al., 2022) or assessed only one domain or a global measure of psychiatric function (Cao et al., 2024; Koval et al., 2022). As such, it is important to continue to investigate how psychiatric features contribute to HD progression profiles in HD. This Doctoral Thesis lays the groundwork for the evaluation of individual differences in HD profiles. In further juxtaposition to the above studies, **Study 4** includes the premanifest cohort prior to motor symptom onset in clustering, proffering additional prognostic information. In doing so, this framework bears potential

to forecast the trajectory that a premanifest individual may develop, in that individuals with a lower disease burden in a given cluster may exhibit a psychiatric signature similar to more advanced patients in the same cluster. Overall, this approach emphasizes individual differences in the severity of longitudinal multivariate clinical characteristics for real-world patient stratification, with implications for precision medicine.

8.7 General Limitations and Considerations

The specific limitations for each study have been discussed separately in *§ Chapters 4 – 7 | Results*. As such, this section will serve as an overview of some of the general limitations inherent across studies. In brief, these encompass the methodological limitations pertaining to apathy scales, definition of clinically relevant apathy, structural neuroimaging, and the assessment of clinical profiles.

8.7.1 Apathy Scales

Throughout the Doctoral Thesis, the quantification of apathy relied on apathy scales. Unfortunately, even when administered in the presence of a knowledgeable informant, such as a caregiver, these means of evaluation are prone to bias by subjective ratings of apathy (R. Levy, 2012). Furthermore, self-rating scales may be prone to anosognosia. (D. A. Isaacs et al., 2024) In addition, there is great heterogeneity between apathy scales themselves. This includes, for example, different numbers and content of items per scale, which conflating factors are controlled for (e.g., depression or motor disability in the Dimensional Apathy Scale) and which subdimensions of apathy are measured, if at all. When utilizing and validating the LARS-s in the HD population in **Study 1** and **Study 3**, we attempted to augment the generalizability of findings by comparing apathy as measured by the LARS-s and the PBA-s, the latter which was designed for use specifically in HD. In addition, in both **Study 1** and **Study 3**, we demonstrated that the apathy dimensions quantified by the LARS-s were concordant with the triadic model of apathy similar to other three-dimensional scales such as the Dimensional Apathy Scale (Radakovic & Abrahams, 2014) and Apathy Evaluation Scale (Marin et al., 1991). However, it is important to keep in mind that the results of the present studies may not necessarily translate to other work using different scales in HD (Atkins et al., 2021).

Currently, there is not yet a widely accepted objective (e.g., task-based) measure of apathy, although several initiatives are in progress, as reviewed in *§ 8.4.2 Apathy Tasks: Potential for Objective Measurement*. Of note, the delineation between internal states of apathy (e.g., motivation) and external, observable states (e.g., goal-directed behavior) has not been fully defined in the literature. For the purpose of the present Doctoral Thesis, apathy is defined as an observable multidimensional syndrome of quantitative reduction in goal-directed behavior in the absence of depression or reduced consciousness. This permitted the use of apathy evaluation scales in the presence of a knowledgeable informant for assessment of apathy. However, it is possible that the internal (subjective) measures of apathy and behavioral (external, observable) measures of apathy may be different, both qualitatively and neurobiologically (Jeffay et al., 2021).

8.7.2 Clinically Relevant Apathy

The present Doctoral Thesis examined inter-individual variability in HD by evaluating apathy along a spectrum of severity and frequency of symptoms. While this approach allows the assessment of subtle differences in apathy between individuals, it is also important to consider the clinical relevance of apathy, or, in other words, its real-world impact on the individual. In **Study 1**, the proportion of individuals with clinically relevant apathy was calculated based on a previously established cutoff for the LARS-s, derived empirically from a sample of Parkinson's disease patients (Dujardin et al., 2013). Notwithstanding, one study revealed that this cutoff value varied even within the Parkinson's disease population, depending on whether and what combination of depression and neurocognitive disorders were present (Weintraut et al., 2016). The authors concluded that there is no universal threshold value for the LARS that is suitable in all types of patients, even within a given disease population. Nonetheless, although not presented in the main results of the Doctoral Thesis, it is worth noting that the optimal LARS-s cut-off value for clinically relevant apathy was confirmed as -7 in the present HD sample utilizing Youden's index (sensitivity=62%, specificity=72%).

When considering the cut-off for the PBA-s, clinically relevant apathy has been reported as > 2 (Martinez-Horta et al., 2016, 2018), including in **Study 1** and **Study 2**, in contrast to other studies that implement a cut-off of ≥ 2 (Baake, Coppen, et al., 2018; Osborne-

Crowley et al., 2019). While the majority of studies employ the frequency × severity score, including in this Doctoral Thesis, one report utilized severity alone (Ruiz-Idiago et al., 2023). As Ruiz-Idiago and colleagues state, the clinical impact of severe and frequent apathy is not the same as apathy that is very severe, but infrequent, or frequent but mild in severity, and hence warrants distinguishment.

In summary, past work in HD and other neurodegenerative diseases does not present a consistent definition of clinically relevant apathy. Instead, inconsistent cut-offs on various scales have been implemented to study apathy across a range of symptom severity and frequency, thus reducing transdiagnostic comparability (D. S. Miller et al., 2021). As such, a related and notable limitation across studies is the low proportion of clinically relevant apathy (Kos et al., 2016). In the present sample, 52.2% of manifest and 29.4% of premanifest individuals demonstrated clinically relevant apathy as measured by the LARS-s in **Study 1**, which mirrors the estimated prevalence of apathy in HD across studies (Paoli et al., 2017). Still, another limitation of the present Doctoral Thesis can be considered as the lack of specific diagnostic criteria to assess a clinical diagnosis of apathy, which would guarantee a consistent, clinically meaningful, and transdiagnostic quantification of apathy.

8.7.3 Structural Neuroimaging

First and foremost, this Doctoral Thesis was limited to the investigation of structural brain correlates of apathy in HD. While a range of neuroimaging modalities were incorporated to assess microstructural and macrostructural neural correlates, including WM integrity, cross-sectional GMV, and longitudinal atrophy, these changes in brain structure do not necessarily predict brain function or behavior (Di Lazzaro et al., 2021). For example, there is evidence in HD of maintained task-based performance and functional brain connectivity despite atrophy of brain structure, suggesting possible compensatory processes at play (Gregory et al., 2018; Klöppel et al., 2015). Nonetheless, structural brain imaging is still the most accessible neuroimaging technique and has consistently demonstrated multi-site longitudinal changes up to fifteen years prior to symptom onset through to established disease diagnosis (Aylward et al., 2011; Georgiou-Karistianis, Gray, et al., 2013; Tabrizi et al., 2011).

The present Doctoral Thesis demonstrated that apathy was significantly related to structural deficits in HD (**Studies 1**, **2**, and **3**). In the broader literature, a relationship between apathy and deterioration in functional neuroimaging metrics has also been demonstrated (Ceccarini et al., 2019; Martinez-Horta et al., 2018; Nair et al., 2022; Sampedro et al., 2019). Taken together, these results suggest that apathy is significantly related with both structural and functional disruptions in HD.

Next, controls were included in only **Study 1** to assess differences in structural connectivity compared to HD patients. As a result, the association between apathy and WM microstructural connectivity in controls was not evaluated. As such, one limitation of the Doctoral Thesis is how specific these WM and GMV variations are for apathy in HD, as opposed to apathy as can be extrapolated to the general population.

Lastly, whenever possible, this Doctoral Thesis invoked a whole-brain approach, such as in **Study 2 and 3**. However, by necessity, the deterministic tractography results of **Study 1** depended on isolating specific ROIs, either manually or via parcellation atlases. By nature, ROI studies are hypothesis-driven and thus carry inherent bias and reduced specificity, as other tracts that were not tested may also underlie apathy dimensions. Nonetheless, the fact that distinct relationships were revealed between apathy dimensions and the three tracts studied (i.e., not all tracts related with all apathy dimensions), substantiates the robustness of the results.

8.7.4 Clinical Profiles

Finally, and as alluded to above in *§ 8.7.2 Clinically Relevant Apathy*, the focus of this Doctoral Thesis was on individual differences in apathy profiles across as spectrum of symptom severity. In light of this, most of the studies did not examine group differences within HD beyond the standard delineation of premanifest and manifest. For example, in **Study 1** and **Study 2**, the relationship between apathy severity and brain biomarkers was studied as a continuum to elucidate inter-individual variability in apathy profiles. Meanwhile, in **Study 3**, apathy profiles were characterized based on the distribution of loadings, or factor scores, that individuals demonstrated along the three empirically defined dimensions of apathy: cognitive, auto-activation deficit, and emotional. These

results did elucidate distinct neural substrates for each apathy dimension. Nonetheless, these studies did not directly test for the existence of patient subgroups.

This opened the door to **Study 4**, which leveraged a clustering approach to stratify individuals according to their longitudinal psychiatric trajectories, while maintaining the numerical information of each variable (as opposed to the traditional categorical approach). However, there was an unfortunate lack of longitudinal LARS-s data that precluded assessment of the progression of apathy dimensions in HD over time. As such, the clustering analysis of **Study 4** aimed to instead characterize the psychiatric disease trajectories of HD, shedding light on the interrelation of apathy with other prominent psychiatric features over time.

This methodology elucidated two main psychiatric signatures in the present sample, contributing important knowledge regarding clinical profiles in HD. At the same time, the relatively small sample size (N = 47) is a limitation throughout the Doctoral Thesis. Thus, in addition to the future directions that will be proposed in the closing subsections, it is also important to bear in mind the value of replicating these studies, especially clustering analysis, in larger, multi-center databases.

8.8 Future Directions

8.8.1 Operationalizaing Apathy

At large, future directions for the measurement of apathy must include the operationalization of dimensional apathy criteria for implementation in clinical practice (D. S. Miller et al., 2021), administration of diagnostic criteria in research and clinical settings, and validation of existing apathy assessment scales as well as novel objective apathy measures and tasks. For example, there is limited research on the validation of the apathy subdomain of the Neuropsychiatric Inventory in neurodegenerative disease, yet the scale is widely utilized in clinical research (Kaufer et al., 2000; Leentjens et al., 2008; Wood et al., 2000).

When considering the validation of apathy scales, it is important to effectuate both a psychometric and a clinimetric approach (Carrozzino, 2019). In brief, the traditional psychometric approach assesses reliability, validity, and internal consistency of a scale. Meanwhile, a clinimetric approach prioritizes the clinical validity of a rating scale, rather than simply statistical significance. In **Study 3**, we incorporated both psychometrics and clinimetrics, the latter with tests of clinical validity, namely convergent validity between the LARS-s and PBA-s apathy scores and discriminant validity with PBA-s depression. **Studies 1 – 4** also examined symptom severity and **Study 1** discriminated between clinically apathetic individuals and healthy controls using designated cut-offs. Other clinimetric variables that must be investigated in future studies encompass the following: sensitivity and specificity based on clinician experience and diagnostic criteria (rather than the psychometric ROC (receiver-operating characteristic) curve), side effects of medications, and potential for screening.

In addition, it is crucial that apathy be prioritized as a primary endpoint in clinical trials. For this, apathy scales (or preferably objective apathy measures in the near future) must be sensitive to change (Mohammad et al., 2018). To this end, the Diagnostic Criteria for Apathy was developed to provide a standardized definition of apathy that incorporates multiple apathy dimensions (Lanctôt et al., 2021), as described in *§ 1.3.1 Diagnostic Criteria for Apathy*. So far, the Diagnostic Criteria for Apathy has been found to significantly correlate with Neuropsychiatric Inventory scores (Mulin et al., 2011). Additional studies validated the full-length LARS against the Neuropsychiatric Inventory apathy score (Drijgers et al., 2010) and the diagnostic accuracy of the Dimensional Apathy Scale against the gold standard Apathy Evaluation Scale (Radakovic, Gray, et al., 2020; Raimo et al., 2020). However, to the author's knowledge, the only direct comparison between the LARS-s and Diagnostic Criteria for Apathy was tested in the original paper in Parkinson's disease (Dujardin et al., 2013). Future studies should determine the clinical sensitivity and specificity of the LARS-s in relation to these diagnostic criteria in other disease populations. This would therefore promote apathy case ascertainment and facilitate intervention studies to assess change in response to treatment. Overall, defining consistent criteria for apathy in neurocognitive disorders would contribute to more optimal clinical trial design and may elucidate apathy profiles for selection in clinical trials.

Of note, Tabrizi and colleagues (2022) recently devised the HD Integrated Staging System, a new framework for disease staging that is comprised of four stages and incorporates neuroimaging and clinical data in addition to genetic information (Tabrizi et al., 2022). The designated clinical landmarks included motor, cognitive (i.e., Symbol Digit Modalities Test), and functional data, but no psychiatric features. Given that apathy is a common and progressive feature of HD and relates with neurodegeneration, as exemplified throughout this Doctoral Thesis, future work may also examine how apathy may potentially serve as an additional marker in the HD staging process.

8.8.2 Neurocircuitry of Apathy

At present, the neurocircuitry of apathy, from large-scale structural and functional correlates to neuromodulators at the molecular and genetic level, is incompletely understood. It is essential that future research continue to elucidate the neural basis of dimensional apathy as a distinct entity (i.e., separable from depression and global cognitive impairment) with the aim of identifying similarities and differences in apathy profiles across neurocognitive disorders. In a similar vein, it is also necessary to carry out comparisons of the neural circuits of clinically relevant apathy with otherwise healthy controls.

Regarding neuroimaging modalities, future research can utilize novel neuroimaging techniques, such as connectome-based methods. As an example, structural covariance networks have been related to cognitive symptoms in Alzheimer's disease and behavioral variant frontotemporal dementia (Tetreault et al., 2020). In addition, dynamic causal modeling has already been used to identify effective connectivity (as opposed to simple statistical correlation) based on resting-state networks in relation to apathy in HD (Nair et al., 2022) and Parkinson's disease (Kahan et al., 2014). Combining emerging objective apathy tests with task-based functional neuroimaging may corroborate the functional role of existing structural neural correlates identified in **Study 1** and **Study 3**, as well as possibly elucidate new regions of brain function implicated in apathy dimensions.

In addition, it is of interest to tease apart the neural mechanisms of various components of the neurocognitive framework for apathy, including reward valuation, task monitoring, and action execution in pursuit of reward. Already, whole-brain functional connectivity

analysis during a gambling task elucidated a significant reduction in brain activity in the left ventral striatum of apathetic HD gene-expansion carriers compared to controls during reward processing, which was not exhibited in non-apathetic HD individuals (Bikou et al., 2024). This work has recently been extended to incorporate apathy subdimensions.

At a molecular level, the connectivity between putative apathy circuits is effectuated by an array of neuromodulators, such as dopamine, acetylcholine, and serotonin. Dopamine depletion in the mesocorticolimbic system has been related with emotional blunting, an aspect of emotional apathy (Pagonabarraga et al., 2015). Administering dopamine agonists has proven effective in rescuing reward sensitivity following bilateral globus pallidal lesions and improving apathy in Parkinson's disease (Adam et al., 2013; Blundo & Gerace, 2015). Meanwhile, dopamine is implicated in decision-making and strategy formation (Friston et al., 2014; Kurniawan et al., 2011), both of which are relevant processes in cognitive apathy. Overall, the involvement of various neurotransmitters in distinct apathy subdimensions bears implications for treatment and deserves further investigation. Finally, further research should interrogate the relationship between apathy and other biomarkers of HD progression, such as neurofilament light chain, which has already been related with behavioral symptoms in HD (Byrne et al., 2017; Sampedro et al., 2021).

In conclusion, ongoing research of the structural and functional networks involved in apathy dimensions bears promise for the development of new therapeutic targets. Likewise, there is potential for the establishment of reliable biomarkers to inform disease prognosis and response to treatment. Through these future studies, there is the possibility of advancing preventive precision medicine.

8.8.3 Clustering Disease Profiles

When considering individual differences in HD, one approach involves the stratification of patients into subgroups using clustering methodology, as was carried out in **Study 4**. Future work could employ similar methodology to evaluate longitudinal trajectories of apathy dimensions over time, in HD as well as in other neurological populations, as such work has not yet been carried out. This, in turn, could provide further evidence for the time point at which different apathy dimensions first present. For example, **Study 1**

evinced that premanifest individuals demonstrated significantly greater levels of auto-activation deficit than controls. Yet, whether the emotional, cognitive, or behavioral dimensions arise earliest in the disease process (i.e., in premanifest individuals), or in what combination, is still a subject of debate (Atkins et al., 2020). Additionally, future study of the interrelation of apathy with other psychiatric disturbances, such as disinhibition, may substantiate that these processes can co-occur at the individual level (L. M. Jenkins et al., 2022).

Lastly, incorporating neuroimaging data in relation to clinical features has previously been demonstrated in HD (Giannoula et al., 2024), and could be extended to include analysis of apathy dimensions as well as the relationship between apathy and other clinical variables. Given recent advancements in machine learning techniques, as well as the augmentation of HD multi-center neuroimaging databases, such as REGISTRY and Enroll-HD (Landwehrmeyer et al., 2016; van Duijn et al., 2014), neuroimaging bears great potential for extended utilization beyond the research sphere. Indeed, brain biomarkers may soon assume a role in daily clinical practice, thereby informing differential diagnoses, monitoring clinical progression and treatment effects, and developing new therapeutic targets for specific patient cohorts (Steffens et al., 2022; Tabrizi et al., 2022).

Chapter 9
Conclusions

Chapter 9 | Conclusions

- The **short-Lille Apathy Rating Scale** can be employed to quantify apathy along its three dimensions in Huntington's disease, with sufficient reliability and clinical validity in distinguishing apathy from depression.

- Like many other neurocognitive disorders, apathy in Huntington's disease follows the **three-dimensional model**, comprised of cognitive apathy, auto-activation deficit, and emotional apathy.

- The apathy profile represented in Huntington's disease is defined by **cognitive apathy and auto-activation deficit** (e.g., behavioral) dimensions, with auto-activation deficit arising even in premanifest individuals.

- Severity in specific apathy dimensions in Huntington's disease can be traced to reduced white matter microstructural connectivity in discrete **frontostriatal circuits** as well as reduced gray matter volume in nodes spanning large-scale motor, cognitive, and limbic networks.

- Change in global apathy is linked with reduced gray matter volume specifically in the right middle cingulate cortex, an area implicated in action-initiation, and longitudinal severity of apathy is predicted by **initial vulnerabilities** in this region.

- Decline in executive dysfunction, but not depression, also **predicts apathy severity** over time in Huntington's disease.

- Considering other **prominent psychiatric features**, longitudinal clustering analysis identified two main psychiatric signatures defined by a dissociation of depression and irritability even in premanifest Huntington's disease, with both trajectories demonstrating increasing perseveration/obsessive-compulsiveness and apathy.

- Ultimately, this Doctoral Thesis substantiates that apathy is a prominent and complex psychiatric feature in **Huntington's disease**, while elucidating neural correlates capable of distinguishing between apathy dimensions and predicting longitudinal progression of apathy over time.

Chapter 10
References

Chapter 10 | References

Aarsland, D., Larsen, J. P., Lim, N. G., Janvin, C., Karlsen, K., Tandberg, E., & Cummings, J. L. (1999). Range of neuropsychiatric disturbances in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *67*(4), 492–496.

Abdollah Zadegan, S., Coco, H. M., Reddy, K. S., Anderson, K. M., Teixeira, A. L., & Stimming, E. F. (2023). Frequency and pathophysiology of apathy in Huntington disease: A systematic review and meta-analysis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *35*(2), 121–132. https://doi.org/10.1176/appi.neuropsych.20220033

Achenbach, J., & Saft, C. (2021). Another perspective on Huntington's disease: Disease burden in family members and pre-manifest HD when compared to genotype-negative participants from ENROLL-HD. *Brain Sciences*, *11*(12), Article 12. https://doi.org/10.3390/brainsci11121621

Acosta-Cabronero, J., Williams, G. B., Pengas, G., & Nestor, P. J. (2010). Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. *Brain*, *133*(2), 529–539. https://doi.org/10.1093/brain/awp257

Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., & Husain, M. (2013). Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. *Cortex*, *49*(5), 1292–1303. https://doi.org/10.1016/j.cortex.2012.04.013

Agüera-Ortiz, L., Gil-Ruiz, N., Cruz-Orduña, I., Ramos-García, I., Osorio, R. S., Valentí-Soler, M., Olazarán-Rodriguez, J., Dobato-Ayuso, J. L., Lanctôt, K., & Martínez-Martín, P. (2015). A novel rating scale for the measurement of apathy in institutionalized persons with dementia: The APADEM-NH. *The American Journal of Geriatric Psychiatry*, *23*(2), 149–159. https://doi.org/10.1016/j.jagp.2013.01.079

Aldaz, T., Nigro, P., Sánchez-Gómez, A., Painous, C., Planellas, L., Santacruz, P., Cámara, A., Compta, Y., Valldeoriola, F., Martí, M. J., & Muñoz, E. (2019). Non-motor symptoms in Huntington's

disease: A comparative study with Parkinson's disease. *Journal of Neurology*, *266*(6), 1340–1350. https://doi.org/10.1007/s00415-019-09263-7

Alexander, M. P., & Stuss, D. T. (2000). Disorders of frontal lobe functioning. *Seminars in Neurology*, *20*(04), 427–438. https://doi.org/10.1055/s-2000-13175

Allman, J. M., Hakeem, A., Erwin, J. M., Nimchinsky, E., & Hof, P. (2006). The anterior cingulate cortex: The evolution of an interface between emotion and cognition. *Annals of the New York Academy of Sciences*, *935*(1), 107–117. https://doi.org/10.1111/j.1749-6632.2001.tb03476.x

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, fifth editon*. American Psychiatric Association.

Anca, M. H., Gazit, E., Loewenthal, R., Ostrovsky, O., Frydman, M., & Giladi, N. (2004). Different phenotypic expression in monozygotic twins with Huntington disease. *American Journal of Medical Genetics Part A*, *124A*(1), 89–91. https://doi.org/10.1002/ajmg.a.20328

Anderson, K. E., Gehl, C. R., Marder, K. S., Beglinger, L. J., & Paulsen, J. S. (2010). Comorbidities of obsessive and compulsive symptoms in Huntington disease. *The Journal of Nervous and Mental Disease*, *198*(5), 334–338. https://doi.org/10.1097/NMD.0b013e3181da852a

Andersson, J. L., Jenkinson, M., & Smith, S. (2007). Non-linear registration, aka spatial normalisation: FMRIB technical report TR07JA2. *FMRIB Analysis Group of the University of Oxford*, *2*, 1–21.

Andersson, S., Krogstad, J. M., & Finset, A. (1999). Apathy and depressed mood in acquired brain damage: Relationship to lesion localization and psychophysiological reactivity. *Psychological Medicine*, *29*(2), 447–456.

Andrews, S. C., Langbehn, D. R., Craufurd, D., Durr, A., Leavitt, B. R., Roos, R. A., Tabrizi, S. J., Stout, J. C., & Investigators, the T.-H. (2020). Apathy predicts rate of cognitive decline over 24

months in premanifest Huntington's disease. *Psychological Medicine*, 1–7. https://doi.org/10.1017/S0033291720000094

Andrieu, S., Coley, N., Rolland, Y., Cantet, C., Arnaud, C., Guyonnet, S., Nourhashemi, F., Grand, A., Vellas, B., & Group, P. (2016). Assessing Alzheimer's disease patients' quality of life: Discrepancies between patient and caregiver perspectives. *Alzheimer's & Dementia*, *12*(4), 427–437. https://doi.org/10.1016/j.jalz.2015.09.003

Ang, Y.-S., Lockwood, P., Apps, M. A. J., Muhammed, K., & Husain, M. (2017). Distinct subtypes of apathy revealed by the Apathy Motivation Index. *PLOS ONE*, *12*(1), e0169938. https://doi.org/10.1371/journal.pone.0169938

Ang, Y.-S., Manohar, S., Plant, O., Kienast, A., Le Heron, C., Muhammed, K., Hu, M., & Husain, M. (2018). Dopamine modulates option generation for behavior. *Current Biology*, *28*(10), 1561-1569.e3. https://doi.org/10.1016/j.cub.2018.03.069

Apostolova, L. G., Akopyan, G. G., Partiali, N., Steiner, C. A., Dutton, R. A., Hayashi, K. M., Dinov, I. D., Toga, A. W., Cummings, J. L., & Thompson, P. M. (2007). Structural correlates of apathy in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *24*(2), 91–97. https://doi.org/10.1159/000103914

Ardila, A., & Lopez, M. V. (1984). Transcortical motor aphasia: One or two aphasias? *Brain and Language*, *22*(2), 350–353. https://doi.org/10.1016/0093-934X(84)90099-3

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Ashburner, J. (2010). *VBM tutorial*. Tech. repWellcome Trust Centre for Neuroimaging, London, UK. http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018

Ashburner, J., & Friston, K. J. (2009). Computing average shaped tissue probability templates. *NeuroImage*, *45*(2), 333–341. https://doi.org/10.1016/j.neuroimage.2008.12.008

Atkins, K. J., Andrews, S. C., Chong, T. T.-J., & Stout, J. C. (2021). Multidimensional apathy: The utility of the Dimensional Apathy Scale in Huntington's disease. *Movement Disorders Clinical Practice*, *8*(3), 361–370. https://doi.org/10.1002/mdc3.13147

Atkins, K. J., Andrews, S. C., Stout, J. C., & Chong, T. T. J. (2024). The effect of Huntington's disease on cognitive and physical motivation. *Brain*, *147*(7), 2449–2458. https://doi.org/10.1093/brain/awae023

Atkins, K. J., Andrews, S. C., Stout, J. C., & Chong, T. T.-J. (2020). Dissociable motivational deficits in pre-manifest Huntington's disease. *Cell Reports Medicine*, *1*(9), 100152. https://doi.org/10.1016/j.xcrm.2020.100152

Atkins, K. J., Friel, C. P., Andrews, S. C., Chong, T. T.-J., Stout, J. C., & Quinn, L. (2022). A qualitative examination of apathy and physical activity in Huntington's and Parkinson's disease. *Neurodegenerative Disease Management*, *12*(3), 129–139. https://doi.org/10.2217/nmt-2021-0047

Avsar, K. B., Weller, R. E., Cox, J. E., Reid, M. A., White, D. M., & Lahti, A. C. (2013). An fMRI investigation of delay discounting in patients with schizophrenia. *Brain and Behavior*, *3*(4), 384–401. https://doi.org/10.1002/brb3.135

Aylward, E. H., Nopoulos, P. C., Ross, C. A., Langbehn, D. R., Pierson, R. K., Mills, J. A., Johnson, H. J., Magnotta, V. A., Juhl, A. R., & Paulsen, J. S. (2011). Longitudinal change in regional brain volumes in prodromal Huntington disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *82*(4), 405–410. https://doi.org/10.1136/jnnp.2010.208264

Aylward, E. H., Sparks, B. F., Field, K. M., Yallapragada, V., Shpritz, B. D., Rosenblatt, A., Brandt, J., Gourley, L. M., Liang, K., Zhou, H., Margolis, R. L., & Ross, C. A. (2004). Onset and rate of striatal atrophy in preclinical Huntington disease. *Neurology*, *63*(1), 66–72. https://doi.org/10.1212/01.WNL.0000132965.14653.D1

Azhar, L., Kusumo, R. W., Marotta, G., Lanctôt, K. L., & Herrmann, N. (2022). Pharmacological management of apathy in dementia. *CNS Drugs*, *36*(2), 143–165. https://doi.org/10.1007/s40263-021-00883-0

Baake, V., Coppen, E. M., van Duijn, E., Dumas, E. M., van den Bogaard, S. J. A., Scahill, R. I., Johnson, H., Leavitt, B., Durr, A., Tabrizi, S. J., Craufurd, D., & Roos, R. A. C. (2018). Apathy and atrophy of subcortical brain structures in Huntington's disease: A two-year follow-up study. *NeuroImage: Clinical*, *19*, 66–70. https://doi.org/10.1016/j.nicl.2018.03.033

Baake, V., van Duijn, E., & Roos, R. A. C. (2018). Huntington's disease gene expansion carriers are aware of their degree of apathy. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 183–187. https://doi.org/10.1176/appi.neuropsych.18020031

Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magnetic Resonance in Medicine*, *44*(4), 625–632. https://doi.org/10.1002/1522-2594(200010)44:4<625::AID-MRM17>3.0.CO;2-O

Baudic, S., Maison, P., Dolbeau, G., Boissé, M.-F., Bartolomeo, P., Dalla Barba, G., Traykov, L., & Bachoud-Lévi, A.-C. (2006). Cognitive impairment related to apathy in early Huntington's disease. *Dementia and Geriatric Cognitive Disorders*, *21*(5–6), 316–321. https://doi.org/10.1159/000091523

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—A technical review. *NMR in Biomedicine*, *15*(7–8), 435–455. https://doi.org/10.1002/nbm.782

Bechara, A. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex*, *10*(3), 295–307. https://doi.org/10.1093/cercor/10.3.295

Becker, R. A., Chambers, J. M., & Wilks, A. R. (1988). *The new S language*. Wadsworth & Brooks/Cole.

Beckmann, M., Johansen-Berg, H., & Rushworth, M. F. S. (2009). Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *Journal of Neuroscience*, *29*(4), 1175–1190. https://doi.org/10.1523/JNEUROSCI.3328-08.2009

Beglinger, L. J., Langbehn, D. R., Duff, K., Stierman, L., Black, D. W., Nehl, C., Anderson, K., Penziner, E., & Paulsen, J. S. (2007). Probability of obsessive and compulsive symptoms in Huntington's disease. *Biological Psychiatry*, *61*(3), 415–418. https://doi.org/10.1016/j.biopsych.2006.04.034

Benoit, M., Clairet, S., Koulibaly, P. M., Darcourt, J., & Robert, P. H. (2004). Brain perfusion correlates of the apathy inventory dimensions of Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *19*(9), 864–869. https://doi.org/10.1002/gps.1163

Berridge, K. C. (2004). Motivation concepts in behavioral neuroscience. *Physiology & Behavior*, *81*(2), 179–209. https://doi.org/10.1016/j.physbeh.2004.02.004

Bhatia, K. P., & Marsden, C. D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*, *117*(4), 859–876. https://doi.org/10.1093/brain/117.4.859

Biglan, K. M., Zhang, Y., Long, J. D., Geschwind, M., Kang, G. A., Killoran, A., Lu, W., McCusker, E., Mills, J. A., Raymond, L. A., Testa, C., Wojcieszek, J., & Paulsen, J. S. (2013). Refining the diagnosis of Huntington disease: The PREDICT-HD study. *Frontiers in Aging Neuroscience*, *5*. https://doi.org/10.3389/fnagi.2013.00012

Bikou, V., De Vicente, I., De Paepe, A. E., Garcia-Gorro, C., Rodriguez-Dechicha, N., Vaquer, I., Calopa, M., De Diego-Balaguer, R., & Camara, E. (2024). *Investigating altered limbic reward system in Huntington's disease: Implications for apathy* [Preprint]. Neuroscience. https://doi.org/10.1101/2024.02.13.580195

Blundo, C., & Gerace, C. (2015). Dopamine agonists can improve pure apathy associated with lesions of the prefrontal-basal ganglia functional system. *Neurological Sciences*, *36*(7), 1197–1201. https://doi.org/10.1007/s10072-014-2061-5

Bogdanova, Y., & Cronin-Golomb, A. (2012). Neurocognitive correlates of apathy and anxiety in Parkinson's disease. *Parkinson's Disease*, *2012*, 1–9. https://doi.org/10.1155/2012/793076

Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience*, *9*(2), 141.

Bonnelle, V., Manohar, S., Behrens, T., & Husain, M. (2016). Individual differences in premotor brain systems underlie behavioral apathy. *Cerebral Cortex*, bhv247. https://doi.org/10.1093/cercor/bhv247

Bonnelle, V., Veromann, K.-R., Burnett Heyes, S., Lo Sterzo, E., Manohar, S., & Husain, M. (2015). Characterization of reward and effort mechanisms in apathy. *Journal of Physiology-Paris*, *109*(1), 16–26. https://doi.org/10.1016/j.jphysparis.2014.04.002

Bonner-Jackson, A., Long, J. D., Westervelt, H., Tremont, G., Aylward, E., Paulsen, J. S., & The PREDICT-HD Investigators and Coordinators of the Huntington Study Group. (2013). Cognitive and brain reserve in prodromal Huntington's disease. *Journal of the International Neuropsychological Society*, *19*(07), 739–750. https://doi.org/10.1017/S1355617713000507

Boone, K. B., Miller, B. L., Swartz, R., Lu, P., & Lee, A. (2003). Relationship between positive and negative symptoms and neuropsychological scores in frontotemporal dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society*, *9*(5), 698–709. https://doi.org/10.1017/S135561770395003X

Bora, E., Velakoulis, D., & Walterfang, M. (2016). Social cognition in Huntington's disease: A meta-analysis. *Behavioural Brain Research*, *297*, 131–140. https://doi.org/10.1016/j.bbr.2015.10.001

Bortolon, C., Macgregor, A., Capdevielle, D., & Raffard, S. (2018). Apathy in schizophrenia: A review of neuropsychological and neuroanatomical studies. *Neuropsychologia*, *118*, 22–33. https://doi.org/10.1016/j.neuropsychologia.2017.09.033

Bouwens, J. A., van Duijn, E., van der Mast, R. C., Roos, R. A. C., & Giltay, E. J. (2015). Irritability in a prospective cohort of Huntington's disease mutation carriers. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(3), 206–212. https://doi.org/10.1176/appi.neuropsych.14030051

Brodaty, H., & Connors, M. H. (2020). Pseudodementia, pseudo-pseudodementia, and pseudodepression. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *12*(1), e12027. https://doi.org/10.1002/dad2.12027

Brooks, M. E., Kristensen, K., Benthem, K. J. van, Magnusson, A., Berg, C. W., Nielsen, A., Skaug, H. J., Mächler, M., & Bolker, B. M. (2017). GlmmTMB balances speed and flexibility among

packages for zero-inflated generalized linear mixed modeling. *The R Journal*, *9*(2), 378–400.

Brown, D. S., Barrett, M. J., Flanigan, J. L., & Sperling, S. A. (2019). Clinical and demographic correlates of apathy in Parkinson's disease. *Journal of Neurology*, *266*(2), 507–514. https://doi.org/10.1007/s00415-018-9166-3

Bruen, P. D., McGeown, W. J., Shanks, M. F., & Venneri, A. (2008). Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain: A Journal of Neurology*, *131*(Pt 9), 2455–2463. https://doi.org/10.1093/brain/awn151

Burgon, C., Goldberg, S. E., van der Wardt, V., Brewin, C., & Harwood, R. H. (2021). Apathy measures in older adults and people with dementia: A systematic review of measurement properties using the COSMIN methodology. *Dementia and Geriatric Cognitive Disorders*, *50*(2), 111–123. https://doi.org/10.1159/000515678

Burnham, K., & Anderson, D. (2002). *Model selection and multimodal inference: A practical information-theoretic approach* (2nd ed.). Springer.

Burns, A., Folstein, S., Brandt, J., & Folstein, M. (1990). Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *The Journal of Nervous and Mental Disease*, *178*(1), 20.

Byrne, L. M., Rodrigues, F. B., Blennow, K., Durr, A., Leavitt, B. R., Roos, R. A. C., Scahill, R. I., Tabrizi, S. J., Zetterberg, H., Langbehn, D., & Wild, E. J. (2017). Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: A retrospective cohort analysis. *The Lancet Neurology*, *16*(8), 601–609. https://doi.org/10.1016/S1474-4422(17)30124-2

Calabrese, J. R., Fava, M., Garibaldi, G., Grunze, H., Krystal, A. D., Laughren, T., Macfadden, W., Marin, R., Nierenberg, A. A., & Tohen, M. (2014). Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders. *Journal of Affective Disorders*, *168*, 439–451. https://doi.org/10.1016/j.jad.2014.06.056

Callaghan, J., Stopford, C., Arran, N., Boisse, M.-F., Coleman, A., Santos, R. D., Dumas, E. M., Hart, E. P., Justo, D., Owen, G., Read, J., Say, M. J., Durr, A., Leavitt, B. R., Roos, R. A. C., Tabrizi, S. J., Bachoud-Levi, A.-C., Bourdet, C., van Duijn, E., & Craufurd, D. (2015). Reliability and factor structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(1), 59–64. https://doi.org/10.1176/appi.neuropsych.13070169

Camacho, M., Barker, R. A., & Mason, S. L. (2018). Apathy in Huntington's disease: A review of the current conceptualization. *Journal of Alzheimer's Disease & Parkinsonism*, *08*(02). https://doi.org/10.4172/2161-0460.1000431

Cammisuli, D. M., & Crow, S. (2018). Spatial disorientation and executive dysfunction in elderly nondemented patients with Parkinson's disease. *Neuropsychiatric Disease and Treatment*, 2531–2539.

Cao, L.-X., Yin, J.-H., Du, G., Yang, Q., & Huang, Y. (2024). Identifying and verifying Huntington's disease subtypes: Clinical features, neuroimaging, and cytokine changes. *Brain and Behavior*, *14*(3), e3469. https://doi.org/10.1002/brb3.3469

Carlozzi, N. E., Miciura, A., Migliore, N., & Dayalu, P. (2014). Understanding the outcomes measures used in Huntington disease pharmacological trials: A systematic review. *Journal of Huntington's Disease*, *3*(3), 233–252. https://doi.org/10.3233/JHD-140115

Caron, N. S., Dorsey, E. R., & Hayden, M. R. (2018). Therapeutic approaches to Huntington disease: From the bench to the clinic. *Nature Reviews Drug Discovery*, *17*(10), 729–750. https://doi.org/10.1038/nrd.2018.133

Carrozzino, D. (2019). Clinimetric approach to rating scales for the assessment of apathy in Parkinson's disease: A systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *94*, 109641. https://doi.org/10.1016/j.pnpbp.2019.109641

Catani, M., Dell'Acqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., Valabregue, R., & Thiebaut de Schotten, M. (2012). Short frontal lobe connections of the human brain. *Cortex*, *48*(2), 273–291. https://doi.org/10.1016/j.cortex.2011.12.001

Catani, M., Howard, R. J., Pajevic, S., & Jones, D. K. (2002). Virtual in vivo interactive dissection of white matter fasiculi in the human brain. *NeuroImage*, *17*, 77–94. https://doi.org/10.1006/nimg.2002.1136

Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, *44*(8), 1105–1132. https://doi.org/10.1016/j.cortex.2008.05.004

Cathomas, F., Hartmann, M. N., Seifritz, E., Pryce, C. R., & Kaiser, S. (2015). The translational study of apathy—An ecological approach. *Frontiers in Behavioral Neuroscience*, *9*. https://doi.org/10.3389/fnbeh.2015.00241

Ceccarini, J., Ahmad, R., Van De Vliet, L., Casteels, C., Vandenbulcke, M., Vandenberghe, W., & Van Laere, K. (2019). Behavioral symptoms in premanifest Huntington disease correlate with reduced frontal CB_1 R levels. *Journal of Nuclear Medicine*, *60*(1), 115–121. https://doi.org/10.2967/jnumed.118.210393

Cercignani, M., & Bouyagoub, S. (2018). Brain microstructure by multi-modal MRI: Is the whole greater than the sum of its parts? *NeuroImage*, *182*, 117–127. https://doi.org/10.1016/j.neuroimage.2017.10.052

Chase, T. N. (2011). Apathy in neuropsychiatric disease: Diagnosis, pathophysiology, and treatment. *Neurotoxicity Research*, *19*(2), 266–278. https://doi.org/10.1007/s12640-010-9196-9

Chatterjee, A., Anderson, K. E., Moskowitz, C. B., Hauser, W. A., & Marder, K. S. (2005). A comparison of self-report and caregiver assessment of depression, apathy, and irritability in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(3), 378–383. https://doi.org/10.1176/jnp.17.3.378

Chau, S. A., Chung, J., Herrmann, N., Eizenman, M., & Lanctôt, K. L. (2016). Apathy and attentional biases in Alzheimer's disease. *Journal of Alzheimer's Disease*, *51*(3), 837–846. https://doi.org/10.3233/JAD-151026

Chen, P., Guarino, P. D., Dysken, M. W., Pallaki, M., Asthana, S., Llorente, M. D., Love, S., Vertrees, J. E., Schellenberg, G. D., & Sano, M. (2018). Neuropsychiatric symptoms and caregiver burden in individuals with Alzheimer's disease: The TEAM-AD VA Cooperative study. *Journal of Geriatric Psychiatry and Neurology*, *31*(4), 177–185. https://doi.org/10.1177/0891988718783897

Chong, T. T.-J., Bonnelle, V., & Husain, M. (2016). Chapter 4. Quantifying motivation with effort-based decision-making paradigms in health and disease. In *Progress in Brain Research* (Vol. 229, pp. 71–100).

Chow, T. W., Binns, M. A., Cummings, J. L., Lam, I., Black, S. E., Miller, B. L., Freedman, M., Stuss, D. T., & van Reekum, R. (2009). Apathy symptom profile and behavioral associations in frontotemporal dementia vs. Alzheimer's disease. *Archives of Neurology*, *66*(7), 888–893. https://doi.org/10.1001/archneurol.2009.92

Clarke, D. E., Ko, J. Y., Kuhl, E. A., van Reekum, R., Salvador, R., & Marin, R. S. (2011). Are the available apathy measures reliable and valid? A review of the psychometric evidence. *Journal of Psychosomatic Research*, *70*(1), 73–97. https://doi.org/10.1016/j.jpsychores.2010.01.012

Cognat, E., Lagarde, J., Decaix, C., Hainque, E., Azizi, L., Gaura-Schmidt, V., Mesnage, V., & Levy, R. (2010). "Habit" gambling behaviour caused by ischemic lesions affecting the cognitive territories of the basal ganglia. *Journal of Neurology*, *257*(10), 1628–1632. https://doi.org/10.1007/s00415-010-5579-3

Cohen, J. (1977). Chapter 2—The t test for means. In *Statistical Power Analysis for the Behavioral Sciences (Revised Edition)* (pp. 19–74). Academic Press. https://doi.org/10.1016/B978-0-12-179060-8.50007-4

Cohen, J. D., Botvinick, M., & Carter, C. S. (2000). Anterior cingulate and prefrontal cortex: Who's in control? *Nature Neuroscience*, *3*(5), 421–423. https://doi.org/10.1038/74783

Connors, M. H., Teixeira-Pinto, A., & Loy, C. T. (2023). Apathy and depression in Huntington's disease: Distinct longitudinal trajectories and clinical correlates. *The Journal of*

Neuropsychiatry and Clinical Neurosciences, *35*(1), 69–76. https://doi.org/10.1176/appi.neuropsych.21070191

Considine, C. M., Rossetti, M. A., Del Bene, V. A., Anderson, K., Anderson, S. A., Celka, A. S., Edmondson, M. C., Nelson-Sheese, A. L., Piccolino, A., Teixeira, A. L., & Stout, J. C. (2023). Huntington Study Group's Neuropsychology Working Group: Implementing non-motor diagnostic criteria. *Movement Disorders Clinical Practice*, *10*(12), 1714–1724. https://doi.org/10.1002/mdc3.13910

Corbo, I., & Casagrande, M. (2022). Higher-level executive functions in healthy elderly and Mild Cognitive Impairment: A systematic review. *Journal of Clinical Medicine*, *11*(5), 1204.

Craig, M. C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., Picchioni, M., McGuire, P. K., Fahy, T., & Murphy, D. G. M. (2009). Altered connections on the road to psychopathy. *Molecular Psychiatry*, *14*(10), 946–953. https://doi.org/10.1038/mp.2009.40

Craufurd, D., Thompson, J. C., & Snowden, J. S. (2001). Behavioral changes in Huntington Disease. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *14*(4), 219–226.

Cruickshank, T. M., Thompson, J. A., D, J. F. D., Reyes, A. P., Bynevelt, M., Georgiou-Karistianis, N., Barker, R. A., & Ziman, M. R. (2015). The effect of multidisciplinary rehabilitation on brain structure and cognition in Huntington's disease: An exploratory study. *Brain and Behavior*, *5*(2), e00312. https://doi.org/10.1002/brb3.312

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*(8), 873–880. https://doi.org/10.1001/archneur.1993.00540080076020

Cummings, J. L. (1997). The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*, *48*(Issue 5, Supplement 6), 10S-16S. https://doi.org/10.1212/WNL.48.5_Suppl_6.10S

Cummings, J. L., Friedman, J. H., Garibaldi, G., Jones, M., Macfadden, W., Marsh, L., & Robert, P. H. (2015). Apathy in neurodegenerative diseases: Recommendations on the design of clinical trials. *Journal of Geriatric Psychiatry and Neurology*, *28*(3), 159–173. https://doi.org/10.1177/0891988715573534

Cummings, J. L., Lanctot, K., Grossberg, G., & Ballard, C. (2024). Progress in pharmacologic management of neuropsychiatric syndromes in neurodegenerative disorders: A review. *JAMA Neurology*, *81*(6), 645. https://doi.org/10.1001/jamaneurol.2024.0586

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*, *44*(12), 2308–2308. https://doi.org/10.1212/WNL.44.12.2308

Cunnington, R., Windischberger, C., Deecke, L., & Moser, E. (2002). The preparation and execution of self-initiated and externally-triggered movement: A study of event-related fMRI. *NeuroImage*, *15*(2), 373–385. https://doi.org/10.1006/nimg.2001.0976

Dale, M., & van Duijn, E. (2015). Anxiety in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(4), 262–271. https://doi.org/10.1176/appi.neuropsych.14100265

David, R., Mulin, E., Friedman, L., Le Duff, F., Cygankiewicz, E., Deschaux, O., Garcia, R., Yesavage, J. A., Robert, P. H., & Zeitzer, J. M. (2012). Decreased daytime motor activity associated with apathy in Alzheimer disease: An actigraphic study. *The American Journal of Geriatric Psychiatry*, *20*(9), 806–814. https://doi.org/10.1097/JGP.0b013e31823038af

Davidson, R. J., Putnam, K. M., & Larson, C. L. (2000). Dysfunction in the neural circuitry of emotion regulation–A possible prelude to violence. *Science*, *289*(5479), 591–594.

Davis, M.-C., Hill, A. T., Fitzgerald, P. B., Bailey, N. W., Sullivan, C., Stout, J. C., & Hoy, K. E. (2022). *Medial prefrontal transcranial alternating current stimulation for apathy in Huntington's disease* [Preprint]. Neurology. https://doi.org/10.1101/2022.08.29.22279310

de Diego-Balaguer, R., Schramm, C., Rebeix, I., Dupoux, E., Durr, A., Brice, A., Charles, P., Cleret de Langavant, L., Youssov, K., Verny, C., Damotte, V., Azulay, J.-P., Goizet, C., Simonin, C., Tranchant, C., Maison, P., Rialland, A., Schmitz, D., Jacquemot, C., … the French Speaking Huntington Group. (2016). COMT Val158Met polymorphism modulates Huntington's disease progression. *PLOS ONE*, *11*(9), e0161106. https://doi.org/10.1371/journal.pone.0161106

De Paepe, A. E., Ara, A., Garcia-Gorro, C., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., Diego-Balaguer, R. de, & Camara, E. (2021). Gray matter vulnerabilities predict longitudinal development of apathy in Huntington's disease. *Movement Disorders*, *36*(5). https://doi.org/10.1002/mds.28638

De Paepe, A. E., Sierpowska, J., Garcia-Gorro, C., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., de Diego-Balaguer, R., & Camara, E. (2019). White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. *NeuroImage: Clinical*, *24*, 101965. https://doi.org/10.1016/j.nicl.2019.101965

Deiber, M.-P., Passingham, R. E., Colebatch, J. G., Friston, K. J., Nixon, P. D., & Frackowiak, R. S. J. (1991). Cortical areas and the selection of movement: A study with positron emission tomography. *Experimental Brain Research*, *84*(2), 393–402. https://doi.org/10.1007/BF00231461

Dell'Acqua, F., Scifo, P., Rizzo, G., Catani, M., Simmons, A., Scotti, G., & Fazio, F. (2010). A modified damped Richardson–Lucy algorithm to reduce isotropic background effects in spherical deconvolution. *NeuroImage*, *49*(2), 1446–1458. https://doi.org/10.1016/j.neuroimage.2009.09.033

Delmaire, C., Dumas, E. M., Sharman, M. A., van den Bogaard, S. J. A., Valabregue, R., Jauffret, C., Justo, D., Reilmann, R., Stout, J. C., Craufurd, D., Tabrizi, S. J., Roos, R. A. C., Durr, A., & Lehéricy, S. (2013). The structural correlates of functional deficits in early Huntington's disease. *Human Brain Mapping*, *34*(9), 2141–2153. https://doi.org/10.1002/hbm.22055

Den Brok, M. G. H. E., Van Dalen, J. W., Van Gool, W. A., Moll Van Charante, E. P., De Bie, R. M. A., & Richard, E. (2015). Apathy in Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders*, *30*(6), 759–769. https://doi.org/10.1002/mds.26208

Desmurget, M., & Sirigu, A. (2009). A parietal-premotor network for movement intention and motor awareness. *Trends in Cognitive Sciences*, *13*(10), 411–419. https://doi.org/10.1016/j.tics.2009.08.001

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, *118*(1), 279–306. https://doi.org/10.1093/brain/118.1.279

Devos, D., Moreau, C., Maltete, D., Lefaucheur, R., Kreisler, A., Eusebio, A., Defer, G., Ouk, T., Azulay, J.-P., Krystkowiak, P., Witjas, T., Delliaux, M., Destee, A., Duhamel, A., Bordet, R., Defebvre, L., & Dujardin, K. (2014). Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: A double-blind, placebo-controlled, randomised clinical trial. *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(6), 668–674. https://doi.org/10.1136/jnnp-2013-306439

Di Lazzaro, V., Bella, R., Benussi, A., Bologna, M., Borroni, B., Capone, F., Chen, K.-H. S., Chen, R., Chistyakov, A. V., Classen, J., Kiernan, M. C., Koch, G., Lanza, G., Lefaucheur, J.-P., Matsumoto, H., Nguyen, J.-P., Orth, M., Pascual-Leone, A., Rektorova, I., … Ranieri, F. (2021). Diagnostic contribution and therapeutic perspectives of transcranial magnetic stimulation in dementia. *Clinical Neurophysiology*, *132*(10), 2568–2607. https://doi.org/10.1016/j.clinph.2021.05.035

Di, X., Rypma, B., & Biswal, B. B. (2014). Correspondence of executive function related functional and anatomical alterations in aging brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *48*, 41–50. https://doi.org/10.1016/j.pnpbp.2013.09.001

Dickson, S. S., & Husain, M. (2022). Are there distinct dimensions of apathy? The argument for reappraisal. *Cortex*, *149*, 246–256. https://doi.org/10.1016/j.cortex.2022.01.001

Dietz, J., Bradley, M. M., Jones, J., Okun, M. S., Perlstein, W. M., & Bowers, D. (2013). The late positive potential, emotion and apathy in Parkinson's disease. *Neuropsychologia*, *51*(5), 960–966. https://doi.org/10.1016/j.neuropsychologia.2013.01.001

D'Iorio, A., Vitale, C., Piscopo, F., Baiano, C., Falanga, A. P., Longo, K., Amboni, M., Barone, P., & Santangelo, G. (2017). Impact of anxiety, apathy and reduced functional autonomy on

perceived quality of life in Parkinson's disease. *Parkinsonism & Related Disorders*, *43*, 114–117. https://doi.org/10.1016/j.parkreldis.2017.08.003

Domínguez Duque, J. F., Egan, G. F., Gray, M. A., Poudel, G. R., Churchyard, A., Chua, P., Stout, J. C., & Georgiou-Karistianis, N. (2013). Multi-modal neuroimaging in premanifest and early Huntington's disease: 18 month longitudinal data from the IMAGE-HD study. *PLOS ONE*, *8*(9), e74131. https://doi.org/10.1371/journal.pone.0074131

Douaud, G., Behrens, T. E., Poupon, C., Cointepas, Y., Jbabdi, S., Gaura, V., Golestani, N., Krystkowiak, P., Verny, C., Damier, P., Bachoud-Lévi, A.-C., Hantraye, P., & Remy, P. (2009). In vivo evidence for the selective subcortical degeneration in Huntington's disease. *NeuroImage*, *46*(4), 958–966. https://doi.org/10.1016/j.neuroimage.2009.03.044

Drapier, D., Drapier, S., Sauleau, P., Haegelen, C., Raoul, S., Biseul, I., Peron, J., Lallement, F., Rivier, I., Reymann, J. M., Edan, G., Verin, M., & Millet, B. (2006). Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *Journal of Neurology*, *253*(8), 1083–1091. https://doi.org/10.1007/s00415-006-0177-0

Drijgers, R. L., Dujardin, K., Reijnders, J. S. A. M., Defebvre, L., & Leentjens, A. F. G. (2010). Validation of diagnostic criteria for apathy in Parkinson's disease. *Parkinsonism & Related Disorders*, *16*(10), 656–660. https://doi.org/10.1016/j.parkreldis.2010.08.015

Ducharme, S., Price, B. H., & Dickerson, B. C. (2018). Apathy: A neurocircuitry model based on frontotemporal dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, *89*(4), 389–396. https://doi.org/10.1136/jnnp-2017-316277

Duff, K., Paulsen, J. S., Beglinger, L. J., Langbehn, D. R., & Stout, J. C. (2007). Psychiatric symptoms in Huntington's disease before diagnosis: The Predict-HD study. *Biological Psychiatry*, *62*(12), 1341–1346. https://doi.org/10.1016/j.biopsych.2006.11.034

Duff, K., Paulsen, J. S., Beglinger, L. J., Langbehn, D. R., Wang, C., Stout, J. C., Ross, C. A., Aylward, E., Carlozzi, N. E., Queller, S., & Predict-HD Investigators of the Huntington Study Group. (2010). "Frontal" behaviors before the diagnosis of Huntington's disease and their relationship to markers of disease progression: Evidence of early lack of awareness.

Journal of Neuropsychiatry, *22*(2), 196–207. https://doi.org/10.1176/appi.neuropsych.22.2.196

Dujardin, K., Langlois, C., Plomhause, L., Carette, A., Delliaux, M., Duhamel, A., & Defebvre, L. (2014). Apathy in untreated early-stage Parkinson disease: Relationship with other non-motor symptoms. *Movement Disorders*, *29*(14), 1796–1801. https://doi.org/10.1002/mds.26058

Dujardin, K., Sockeel, P., Carette, A.-S., Delliaux, M., & Defebvre, L. (2013). Assessing apathy in everyday clinical practice with the Short-form Lille Apathy Rating Scale. *Movement Disorders*, *28*(14).

Dujardin, K., Sockeel, P., Devos, D., Delliaux, M., Krystkowiak, P., Destée, A., & Defebvre, L. (2007). Characteristics of apathy in Parkinson's disease. *Movement Disorders*, *22*(6), 778–784. https://doi.org/10.1002/mds.21316

Dumas, E. M., van den Bogaard, S. J. A., Hart, E. P., Soeter, R. P., van Buchem, M. A., van der Grond, J., Rombouts, S. A. R. B., & Roos, R. A. C. (2013). Reduced functional brain connectivity prior to and after disease onset in Huntington's disease. *NeuroImage : Clinical*, *2*, 377–384. https://doi.org/10.1016/j.nicl.2013.03.001

Dwyer, D. B., Falkai, P., & Koutsouleris, N. (2018). Machine learning approaches for clinical psychology and psychiatry. *Annual Review of Clinical Psychology*, *14*(1), 91–118. https://doi.org/10.1146/annurev-clinpsy-032816-045037

Eddy, C. M., Parkinson, E. G., & Rickards, H. E. (2016). Changes in mental state and behaviour in Huntington's disease. *The Lancet Psychiatry*, *3*(11), 1079–1086. https://doi.org/10.1016/S2215-0366(16)30144-4

Eddy, C. M., & Rickards, H. E. (2013). Impact of cognitive and behavioural changes on quality of life in Huntington's disease. *Basal Ganglia*, *3*(2), 123–126. https://doi.org/10.1016/j.baga.2013.01.085

Epping, E. A., Kim, J.-I., Craufurd, D., Brashers-Krug, T. M., Anderson, K. E., McCusker, E., Luther, J., Long, J. D., Paulsen, J. S., & PREDICT-HD Investigators and Coordinators of the Huntington

Study Group. (2016). Longitudinal psychiatric symptoms in prodromal Huntington's disease: A decade of data. *American Journal of Psychiatry*, *173*(2), 184–192. https://doi.org/10.1176/appi.ajp.2015.14121551

Epping, E. A., Mills, J. A., Beglinger, L. J., Fiedorowicz, J. G., Craufurd, D., Smith, M. M., Groves, M., Bijanki, K. R., Downing, N., Williams, J. K., Long, J. D., & Paulsen, J. S. (2013). Characterization of depression in prodromal Huntington disease in the neurobiological predictors of HD (PREDICT-HD) study. *Journal of Psychiatric Research*, *47*(10), 1423–1431. https://doi.org/10.1016/j.jpsychires.2013.05.026

Epping, E. A., & Paulsen, J. S. (2011). Depression in the early stages of Huntington disease. *Neurodegenerative Disease Management*, *1*(5), 407. https://doi.org/10.2217/nmt.11.45

Fahn, S., Elton, R., & Members of the UPDRS Development Committee. (1987). The Unified Parkinson's Disease Rating Scale. In *Recent Developments in Parkinson's Disease* (Vol. 2, pp. 153–163). McMellam Health Care Information.

Fava, M., Hwang, I., Rush, A. J., Sampson, N., Walters, E. E., & Kessler, R. C. (2010). The importance of irritability as a symptom of major depressive disorder: Results from the National Comorbidity Survey Replication. *Molecular Psychiatry*, *15*(8), 856–867. https://doi.org/10.1038/mp.2009.20

Fernandez-Matarrubia, M., Matías-Guiu, J. A., Cabrera-Martín, M. N., Moreno-Ramos, T., Valles-Salgado, M., Carreras, J. L., & Matías-Guiu, J. (2018). Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *33*(1), 141–150. https://doi.org/10.1002/gps.4695

Fernandez-Matarrubia, M., Matías-Guiu, J. A., Moreno-Ramos, T., Valles-Salgado, M., Marcos-Dolado, A., García-Ramos, R., & Matías-Guiu, J. (2016). Validation of the Lille's Apathy Rating Scale in very mild to moderate dementia. *The American Journal of Geriatric Psychiatry*, *24*(7), 517–527. https://doi.org/10.1016/j.jagp.2015.09.004

Fitts, W., Massimo, L., Lim, N., Grossman, M., & Dahodwala, N. (2016). Computerized assessment of goal-directed behavior in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *38*(9), 1015–1025. https://doi.org/10.1080/13803395.2016.1184232

François, C., Ripollés, P., Bosch, L., Garcia-Alix, A., Muchart, J., Sierpowska, J., Fons, C., Solé, J., Rebollo, M., Gaitán, H., & Rodriguez-Fornells, A. (2016). Language learning and brain reorganization in a 3.5-year-old child with left perinatal stroke revealed using structural and functional connectivity. *Cortex*, *77*, 95–118. https://doi.org/10.1016/j.cortex.2016.01.010

Frank, M. J. (2011). Computational models of motivated action selection in corticostriatal circuits. *Current Opinion in Neurobiology*, *21*(3), 381–386. https://doi.org/10.1016/j.conb.2011.02.013

Frank, S. (2014). Treatment of Huntington's disease. *Neurotherapeutics*, *11*(1), 153–160. https://doi.org/10.1007/s13311-013-0244-z

Fried, I., Mukamel, R., & Kreiman, G. (2011). Internally generated preactivation of single neurons in human medial frontal cortex predicts volition. *Neuron*, *69*(3), 548–562. https://doi.org/10.1016/j.neuron.2010.11.045

Friedman, J. H., & Meulman, J. J. (2004). Clustering objects on subsets of attributes (with discussion). *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, *66*(4), 815–849. https://doi.org/10.1111/j.1467-9868.2004.02059.x

Friedman, J. H., Trieschmann, M. E., Myers, R. H., & Fernandez, H. H. (2005). Monozygotic twins discordant for Huntington disease after 7 years. *Archives of Neurology*, *62*(6), 995–997. https://doi.org/10.1001/archneur.62.6.995

Friston, K., Schwartenbeck, P., FitzGerald, T., Moutoussis, M., Behrens, T., & Dolan, R. J. (2014). The anatomy of choice: Dopamine and decision-making. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1655), 20130481. https://doi.org/10.1098/rstb.2013.0481

Fritz, N. E., Boileau, N. R., Stout, J. C., Ready, R., Perlmutter, J. S., Paulsen, J. S., Quaid, K., Barton, S., McCormack, M. K., Perlman, S. L., Carlozzi, N. E., Carlozzi, N., Dayalu, P., Kratz, A. L., Schilling, S., Austin, A., Canter, M., Goodnight, S., Miner, J., … Chicago. (2018). Relationships among apathy, health-related quality of life, and function in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 194–201. https://doi.org/10.1176/appi.neuropsych.17080173

Garcia-Gorro, C., Llera, A., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., Beckmann, C. F., de Diego-Balaguer, R., & Camara, E. (2019). Specific patterns of brain alterations underlie distinct clinical profiles in Huntington's disease. *NeuroImage: Clinical*, *23*, 101900. https://doi.org/10.1016/j.nicl.2019.101900

Garcia-Miralles, M., Ooi, J., Ferrari Bardile, C., Tan, L. J., George, M., Drum, C. L., Lin, R. Y., Hayden, M. R., & Pouladi, M. A. (2016). Treatment with the MAO-A inhibitor clorgyline elevates monoamine neurotransmitter levels and improves affective phenotypes in a mouse model of Huntington disease. *Experimental Neurology*, *278*, 4–10. https://doi.org/10.1016/j.expneurol.2016.01.019

Gasquoine, P. G. (2014). Contributions of the insula to cognition and emotion. *Neuropsychology Review*, *24*(2), 77–87. https://doi.org/10.1007/s11065-014-9246-9

Geda, Y. E., Roberts, R. O., Mielke, M. M., Knopman, D. S., Christianson, T. J. H., Pankratz, V. S., Boeve, B. F., Sochor, O., Tangalos, E. G., Petersen, R. C., & Rocca, W. A. (2014). Baseline neuropsychiatric symptoms and the risk of incident Mild Cognitive Impairment: A population-based study. *American Journal of Psychiatry*, *171*(5), 572–581. https://doi.org/10.1176/appi.ajp.2014.13060821

Georgiou, N., Bradshaw, J. L., Chiu, E., Tudor, A., O'Gorman, L., & Phillips, J. G. (1999). Differential clinical and motor control function in a pair of monozygotic twins with Huntington's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *14*(2), 320–325.

Georgiou-Karistianis, N., Gray, M. A., Domínguez D, J. F., Dymowski, A. R., Bohanna, I., Johnston, L. A., Churchyard, A., Chua, P., Stout, J. C., & Egan, G. F. (2013). Automated differentiation of pre-diagnosis Huntington's disease from healthy control individuals based on quadratic discriminant analysis of the basal ganglia: The IMAGE-HD study. *Neurobiology of Disease*, *51*, 82–92. https://doi.org/10.1016/j.nbd.2012.10.001

Georgiou-Karistianis, N., Scahill, R., Tabrizi, S. J., Squitieri, F., & Aylward, E. (2013). Structural MRI in Huntington's disease and recommendations for its potential use in clinical trials. *Neuroscience & Biobehavioral Reviews*, *37*(3), 480–490. https://doi.org/10.1016/j.neubiorev.2013.01.022

Ghazaleh, N., Houghton, R., Palermo, G., Schobel, S. A., Wijeratne, P. A., & Long, J. D. (2021). Ranking the predictive power of clinical and biological features associated with disease progression in Huntington's disease. *Frontiers in Neurology*, *12*, 678484. https://doi.org/10.3389/fneur.2021.678484

Giannoula, A., Centeno, E., Mayer, M.-A., Sanz, F., & Furlong, L. I. (2020). A system-level analysis of patient disease trajectories based on clinical, phenotypic and molecular similarities. *Bioinformatics*, btaa964. https://doi.org/10.1093/bioinformatics/btaa964

Giannoula, A., De Paepe, A. E., Sanz, F., Furlong, L. I., & Camara, E. (2024). *Identifying temporal patterns in the progression of neurodegenerative disease using unsupervised clustering* [Preprint]. medRxiv. https://doi.org/10.1101/2024.02.23.24303255

Giannoula, A., Gutierrez-Sacristán, A., Bravo, Á., Sanz, F., & Furlong, L. I. (2018). Identifying temporal patterns in patient disease trajectories using dynamic time warping: A population-based study. *Scientific Reports*, *8*(1), 4216. https://doi.org/10.1038/s41598-018-22578-1

Gibbons, R. D., Hedeker, D., & DuToit, S. (2010). Advances in analysis of longitudinal data. *Annual Review of Clinical Psychology*, *6*, 79–107. https://doi.org/10.1146/annurev.clinpsy.032408.153550

Gignac, G. E., & Szodorai, E. T. (2016). Effect size guidelines for individual differences researchers. *Personality and Individual Differences*, *102*, 74–78. https://doi.org/10.1016/j.paid.2016.06.069

Gómez-Esteban, J. C., Lezcano, E., Zarranz, J. J., Velasco, F., Garamendi, I., Pérez, T., & Tijero, B. (2007). Monozygotic twins suffering from Huntington's disease show different cognitive and behavioural symptoms. *European Neurology*, *57*(1), 26–30. https://doi.org/10.1159/000097006

Gonçalves, S. de A. B., Caramelli, P., Mariano, L. I., Guimarães, H. C., Gambogi, L. B., Resende, E. de P. F., Teixeira, A. L., & de Souza, L. C. (2020). Apathy in frontotemporal dementia is related to medial prefrontal atrophy and is independent of executive dysfunction. *Brain Research*, *1737*, 146799. https://doi.org/10.1016/j.brainres.2020.146799

Grace, J., & Malloy, P. (2001). Frontal Systems Behavior Scale (FrSBe): Professional manual. *Psychological Assessment Resources*.

Gregory, S., Long, J. D., Klöppel, S., Razi, A., Scheller, E., Minkova, L., Johnson, E. B., Durr, A., Roos, R. A. C., Leavitt, B. R., Mills, J. A., Stout, J. C., Scahill, R. I., Tabrizi, S. J., Rees, G., Investigators, T.-O., Coleman, A., Decolongon, J., Fan, M., … Orth, M. (2018). Testing a longitudinal compensation model in premanifest Huntington's disease. *Brain*, *141*(7), 2156–2166. https://doi.org/10.1093/brain/awy122

Gregory, S., Seunarine, K. K., Stopford, C., Zhang, H., Zhang, J., Orth, M., Durr, A., Roos, R. A. C., Langbehn, D. R., Long, J. D., Johnson, H., Rees, G., Tabrizi, S. J., Craufurd, D., & Track-HD investigators. (2015). Neuropsychiatry and white matter microstructure in Huntington's disease. *Journal of Huntington's Disease*, *4*(3), 239–249. https://doi.org/10.3233/JHD-150160

Grimm, K. J., An, Y., McArdle, J. J., Zonderman, A. B., & Resnick, S. M. (2012). Recent changes leading to subsequent changes: Extensions of multivariate latent difference score models. *Structural Equation Modeling : A Multidisciplinary Journal*, *19*(2), 268–292. https://doi.org/10.1080/10705511.2012.659627

Grossi, D., Santangelo, G., Barbarulo, A. M., Vitale, C., Castaldo, G., Proto, M. G., Siano, P., Barone, P., & Trojano, L. (2013). Apathy and related executive syndromes in dementia associated with Parkinson's disease and in Alzheimer's disease. *Behavioural Neurology*, *27*(4), 515–522. https://doi.org/10.1155/2013/781029

Gruber, A. J., & McDonald, R. J. (2012). Context, emotion, and the strategic pursuit of goals: Interactions among multiple brain systems controlling motivated behavior. *Frontiers in Behavioral Neuroscience*, *6*. https://doi.org/10.3389/fnbeh.2012.00050

Guimarães, H. C., Levy, R., Teixeira, A. L., Beato, R. G., & Caramelli, P. (2008). Neurobiology of apathy in Alzheimer's disease. *Arquivos de Neuro-Psiquiatria*, *66*(2b), 436–443. https://doi.org/10.1590/S0004-282X2008000300035

Gunn, S., Dale, M., Ovaska-Stafford, N., & Maltby, J. (2023). Mental health symptoms among those affected by Huntington's disease: A cross-sectional study. *Brain and Behavior*, *13*(4), e2954. https://doi.org/10.1002/brb3.2954

Gunn, S., Maltby, J., & Dale, M. (2020). Assessing mental health difficulties of persons with Huntington's disease: Does informant presence make a difference? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *32*(3), 244–251. https://doi.org/10.1176/appi.neuropsych.19080181

Haggard, P. (2008). Human volition: Towards a neuroscience of will. *Nature Reviews Neuroscience*, *9*(12), 934–946. https://doi.org/10.1038/nrn2497

Hahn, C., Lim, H.-K., Won, W. Y., Ahn, K. J., Jung, W.-S., & Lee, C. U. (2013). Apathy and white matter integrity in Alzheimer's disease: A whole brain analysis with Tract-Based Spatial Statistics. *PLOS ONE*, *8*(1), e53493. https://doi.org/10.1371/journal.pone.0053493

Hamilton, J. M. (2003). Behavioural abnormalities contribute to functional decline in Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(1), 120–122. https://doi.org/10.1136/jnnp.74.1.120

Hamilton, J. M., Salmon, D. P., Corey-Bloom, J., Gamst, A., Paulsen, J. S., Jerkins, S., Jacobson, M. W., & Peavy, G. (2003). Behavioural abnormalities contribute to functional decline in Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(1), 120–122.

Happy, S. L., Dantcheva, A., Das, A., Zeghari, R., Robert, P., & Bremond, F. (2019). Characterizing the state of apathy with facial expression and motion analysis. *2019 14th IEEE International Conference on Automatic Face & Gesture Recognition (FG 2019)*, 1–8. https://doi.org/10.1109/FG.2019.8756545

Hare, E., Bachoud-Lévi, A.-C., Reilmann, R., Craufurd, D., Busse, M., Rosser, A., & McLauchlan, D. (2022). Cognitive processes of apathy in Huntington's disease show high sensitivity to disease progression. *Clinical Parkinsonism & Related Disorders*, *7*, 100168. https://doi.org/10.1016/j.prdoa.2022.100168

Hare, T. A., Camerer, C. F., Knoepfle, D. T., O'Doherty, J. P., & Rangel, A. (2010). Value computations in ventral medial prefrontal cortex during charitable decision making incorporate input from regions involved in social cognition. *Journal of Neuroscience*, *30*(2), 583–590. https://doi.org/10.1523/JNEUROSCI.4089-09.2010

Haro, J. M., Kahle-Wrobleski, K., Bruno, G., Belger, M., Dell'Agnello, G., Dodel, R., Jones, R. W., Reed, C. C., Vellas, B., Wimo, A., & Argimon, J. M. (2014). Analysis of burden in caregivers of people with Alzheimer's disease using self-report and supervision hours. *The Journal of Nutrition, Health and Aging*, *18*(7), 677–684. https://doi.org/10.1007/s12603-014-0500-x

Harrington, D. L., Long, J. D., Durgerian, S., Mourany, L., Koenig, K., Bonner-Jackson, A., Paulsen, J. S., for the PREDICT-HD Investigators of the Huntington Study Group, & Rao, S. M. (2016). Cross-sectional and longitudinal multimodal structural imaging in prodromal Huntington's disease. *Movement Disorders*, *31*(11), 1664–1675. https://doi.org/10.1002/mds.26803

Harris, K. L., Mason, S. L., & Barker, R. A. (2022). Exploring the predictors of financial impairment in Huntington's disease using the Enroll-HD dataset. *Journal of Neurology*, *269*(7), 3501. https://doi.org/10.1007/s00415-021-10929-4

Heath, C. J., O'Callaghan, C., Mason, S. L., Phillips, B. U., Saksida, L. M., Robbins, T. W., Barker, R. A., Bussey, T. J., & Sahakian, B. J. (2019). A touchscreen motivation assessment evaluated in Huntington's disease patients and R6/1 model mice. *Frontiers in Neurology*, *10*, 858. https://doi.org/10.3389/fneur.2019.00858

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2021). Intellectual curiosity and action initiation are subtypes of apathy affected in Huntington's disease gene expansion carriers. *Alzheimer's & Dementia*, *17*(S6), e050872. https://doi.org/10.1002/alz.050872

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2023). On the association between apathy and deficits of social cognition and executive functions in Huntington's disease. *Journal of the International Neuropsychological Society*, *29*(4), 369–376. https://doi.org/10.1017/S1355617722000364

Hobbs, N. Z., Farmer, R. E., Rees, E. M., Cole, J. H., Haider, S., Malone, I. B., Sprengelmeyer, R., Johnson, H., Mueller, H.-P., Sussmuth, S. D., Roos, R. A. C., Durr, A., Frost, C., Scahill, R. I., Landwehrmeyer, B., & Tabrizi, S. J. (2015). Short-interval observational data to inform clinical trial design in Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *86*(12), 1291–1298. https://doi.org/10.1136/jnnp-2014-309768

Hoffstaedter, F., Grefkes, C., Zilles, K., & Eickhoff, S. B. (2013). The "what" and "when" of self-initiated movements. *Cerebral Cortex*, *23*(3), 520–530. https://doi.org/10.1093/cercor/bhr391

Honrath, P., Dogan, I., Wudarczyk, O., Görlich, K. S., Votinov, M., Werner, C. J., Schumann, B., Overbeck, R. T., Schulz, J. B., Landwehrmeyer, B. G., Gur, R. E., Habel, U., Reetz, K., & the Enroll-HD investigators. (2018). Risk factors of suicidal ideation in Huntington's disease:

Literature review and data from Enroll-HD. *Journal of Neurology*, *265*(11), 2548–2561. https://doi.org/10.1007/s00415-018-9013-6

Hubers, A. A. M., Reedeker, N., Giltay, E. J., Roos, R. A. C., Van Duijn, E., & Van Der Mast, R. C. (2012). Suicidality in Huntington's disease. *Journal of Affective Disorders*, *136*(3), 550–557. https://doi.org/10.1016/j.jad.2011.10.031

Hubers, A. A. M., Van Duijn, E., Roos, R. A. C., Craufurd, D., Rickards, H., Bernhard Landwehrmeyer, G., Van Der Mast, R. C., & Giltay, E. J. (2013). Suicidal ideation in a European Huntington's disease population. *Journal of Affective Disorders*, *151*(1), 248–258. https://doi.org/10.1016/j.jad.2013.06.001

Huntington Study Group. (1996). Unified Huntington's Disease Rating Scale: Reliability and consistency. *Movement Disorders*, *11*(2), 136–142. https://doi.org/10.1002/mds.870110204

Husain, M., & Roiser, J. P. (2018). Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nature Reviews Neuroscience*, *19*(8), 470–484. https://doi.org/10.1038/s41583-018-0029-9

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Isaacs, D. A., Hay, K. R., Hoadley, J., McDonell, K. E., Brown, A. E., Wynn, A., Claassen, D. O., & Gibson, J. (2024). Influence of anosognosia on patient-reported outcomes for psychiatric symptoms and quality of life in Huntington's disease. *Parkinsonism & Related Disorders*, *123*, 106969. https://doi.org/10.1016/j.parkreldis.2024.106969

Isaacs, D., Gibson, J. S., Stovall, J., & Claassen, D. O. (2020). The impact of anosognosia on clinical and patient-reported assessments of psychiatric symptoms in Huntington's disease. *Journal of Huntington's Disease*, *9*(3), 291–302. https://doi.org/10.3233/JHD-200410

Jacobs, M., Hart, E. P., & Roos, R. A. C. (2018). Cognitive performance and apathy predict unemployment in Huntington's disease mutation carriers. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 188–193. https://doi.org/10.1176/appi.neuropsych.17070144

James, C. E., Oechslin, M. S., Van De Ville, D., Hauert, C.-A., Descloux, C., & Lazeyras, F. (2014). Musical training intensity yields opposite effects on grey matter density in cognitive versus sensorimotor networks. *Brain Structure and Function*, *219*(1), 353–366. https://doi.org/10.1007/s00429-013-0504-z

Jao, Y.-L., Algase, D. L., Specht, J. K., & Williams, K. (2016). Developing the Person–Environment Apathy Rating for persons with dementia. *Aging & Mental Health*. https://www.tandfonline.com/doi/abs/10.1080/13607863.2015.1043618

Jeffay, E., Grimes, K. M., & Zakzanis, K. K. (2021). Chapter 8. Apathy and traumatic brain injury. In *Apathy: Clinical and Neuroscientific Perspectives from Neurology and Psychiatry* (p. 138). Oxford University Press.

Jenkins, I. H., Jahanshahi, M., Jueptner, M., Passingham, R. E., & Brooks, D. J. (2000). Self-initiated versus externally triggered movements: II. The effect of movement predictability on regional cerebral blood flow. *Brain*, *123*, 1216–1228.

Jenkins, L. M., Wang, L., Rosen, H., & Weintraub, S. (2022). A transdiagnostic review of neuroimaging studies of apathy and disinhibition in dementia. *Brain*, *145*(6), 1886–1905. https://doi.org/10.1093/brain/awac133

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156. https://doi.org/10.1016/S1361-8415(01)00036-6

Jiang, Y., Kim, S., & Bong, M. (2014). Effects of reward contingencies on brain activation during feedback processing. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00656

Joseph, R. (1999). Frontal lobe psychopathology: Mania, depression, confabulation, catatonia, perseveration, obsessive compulsions, and schizophrenia. *Psychiatry*, *62*(2), 138–172.

Julayanont, P., Heilman, K. M., & McFarland, N. R. (2020). Early-motor phenotype relates to neuropsychiatric and cognitive disorders in Huntington's disease. *Movement Disorders*, *35*(5), 781–788. https://doi.org/10.1002/mds.27980

Julien, C. L., Thompson, J. C., Wild, S., Yardumian, P., Snowden, J. S., Turner, G., & Craufurd, D. (2007). Psychiatric disorders in preclinical Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(9), 939–943. https://doi.org/10.1136/jnnp.2006.103309

Kable, J. W., & Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, *10*(12), 1625–1633. https://doi.org/10.1038/nn2007

Kahan, J., Urner, M., Moran, R., Flandin, G., Marreiros, A., Mancini, L., White, M., Thornton, J., Yousry, T., Zrinzo, L., Hariz, M., Limousin, P., Friston, K., & Foltynie, T. (2014). Resting state functional MRI in Parkinson's disease: The impact of deep brain stimulation on 'effective' connectivity. *Brain*, *137*(4), 1130–1144. https://doi.org/10.1093/brain/awu027

Kassubek, J., Bernhard Landwehrmeyer, G., Ecker, D., Juengling, F. D., Muche, R., Schuller, S., Weindl, A., & Peinemann, A. (2004). Global cerebral atrophy in early stages of Huntington's disease: Quantitative MRI study. *NeuroReport*, *15*(2), 363–365.

Kaufer, D. I., Cummings, J. L., Ketchel, P., Smith, V., MacMillan, A., Shelley, T., Lopez, O. L., & DeKosky, S. T. (2000). Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(2), 233–239. https://doi.org/10.1176/jnp.12.2.233

Kawagoe, T., Onoda, K., & Yamaguchi, S. (2017). Apathy and executive function in healthy elderly—Resting state fMRI study. *Frontiers in Aging Neuroscience*, *9*, 124. https://doi.org/10.3389/fnagi.2017.00124

Kempnich, C. L., Andrews, S. C., Fisher, F., Wong, D., Georgiou-Karistianis, N., & Stout, J. C. (2018). Emotion recognition correlates with social-neuropsychiatric dysfunction in Huntington's disease. *Journal of the International Neuropsychological Society*, *24*(5), 417–423. https://doi.org/10.1017/S1355617717001308

Killoran, A., Biglan, K. M., Jankovic, J., Eberly, S., Kayson, E., Oakes, D., Young, A. B., & Shoulson, I. (2013). Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. *Neurology*, *80*(22), 2022–2027. https://doi.org/10.1212/WNL.0b013e318294b304

Kim, J., Long, J. D., Mills, J. A., McCusker, E., & Paulsen, J. S. (2015). Multivariate clustering of progression profiles reveals different depression patterns in prodromal Huntington disease. *Neuropsychology*, *29*(6), 949–960. https://doi.org/10.1037/neu0000199

Kingma, E. M., van Duijn, E., Timman, R., van der Mast, R. C., & Roos, R. A. C. (2008). Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. *General Hospital Psychiatry*, *30*(2), 155–161. https://doi.org/10.1016/j.genhosppsych.2007.11.005

Kipps, C. M. (2005). Progression of structural neuropathology in preclinical Huntington's disease: A tensor based morphometry study. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(5), 650–655. https://doi.org/10.1136/jnnp.2004.047993

Kirkwood, S. C., Siemers, E., Viken, R., Hodes, M. E., Conneally, P. M., Christian, J. C., & Foroud, T. (2002). Longitudinal personality changes among presymptomatic Huntington disease gene carriers. *Cognitive and Behavioral Neurology*, *15*(3), 192–197.

Kirsch-Darrow, L., Marsiske, M., Okun, M. S., Bauer, R., & Bowers, D. (2011). Apathy and depression: Separate factors in Parkinson's disease. *Journal of the International Neuropsychological Society*, *17*(06), 1058–1066. https://doi.org/10.1017/S1355617711001068

Kirsch-Darrow, L., Zahodne, L. B., Hass, C., Mikos, A., Okun, M. S., Fernandez, H. H., & Bowers, D. (2009). How cautious should we be when assessing apathy with the Unified Parkinson's

Disease Rating Scale? *Movement Disorders*, *24*(5), 684–688. https://doi.org/10.1002/mds.22437

Klöppel, S., Gregory, S., Scheller, E., Minkova, L., Razi, A., Durr, A., Roos, R. A. C., Leavitt, B. R., Papoutsi, M., Landwehrmeyer, G. B., Reilmann, R., Borowsky, B., Johnson, H., Mills, J. A., Owen, G., Stout, J., Scahill, R. I., Long, J. D., Rees, G., & Tabrizi, S. J. (2015). Compensation in preclinical Huntington's disease: Evidence from the Track-On HD study. *EBioMedicine*, *2*(10), 1420–1429. https://doi.org/10.1016/j.ebiom.2015.08.002

Ko, J., Furby, H., Ma, X., Long, J. D., Lu, X.-Y., Slowiejko, D., & Gandhy, R. (2023). Clustering and prediction of disease progression trajectories in Huntington's disease: An analysis of Enroll-HD data using a machine learning approach. *Frontiers in Neurology*, *13*, 1034269. https://doi.org/10.3389/fneur.2022.1034269

Koechlin, E. (2016). Prefrontal executive function and adaptive behavior in complex environments. *Current Opinion in Neurobiology*, *37*, 1–6. https://doi.org/10.1016/j.conb.2015.11.004

König, A., Linz, N., Zeghari, R., Klinge, X., Tröger, J., Alexandersson, J., & Robert, P. (2019). Detecting apathy in older adults with cognitive disorders using automatic speech analysis. *Journal of Alzheimer's Disease*, *69*(4), 1183–1193. https://doi.org/10.3233/JAD-181033

Koolschijn, P. C. M. P., Haren, N. E. M. van, Lensvelt-Mulders, G. J. L. M., Pol, H. E. H., & Kahn, R. S. (2009). Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Human Brain Mapping*, *30*(11), 3719–3735. https://doi.org/10.1002/hbm.20801

Kos, C., Klaasen, N. G., Marsman, J.-B. C., Opmeer, E. M., Knegtering, H., Aleman, A., & Van Tol, M.-J. (2017). Neural basis of self-initiative in relation to apathy in a student sample. *Scientific Reports*, *7*(1), 3264. https://doi.org/10.1038/s41598-017-03564-5

Kos, C., van Tol, M.-J., Marsman, J.-B. C., Knegtering, H., & Aleman, A. (2016). Neural correlates of apathy in patients with neurodegenerative disorders, acquired brain injury, and

psychiatric disorders. *Neuroscience & Biobehavioral Reviews*, *69*, 381–401. https://doi.org/10.1016/j.neubiorev.2016.08.012

Koval, I., Dighiero-Brecht, T., Tobin, A. J., Tabrizi, S. J., Scahill, R. I., Tezenas Du Montcel, S., Durrleman, S., & Durr, A. (2022). Forecasting individual progression trajectories in Huntington disease enables more powered clinical trials. *Scientific Reports*, *12*(1), 18928. https://doi.org/10.1038/s41598-022-18848-8

Krogias, C., Strassburger, K., Eyding, J., Gold, R., Norra, C., Juckel, G., Saft, C., & Ninphius, D. (2011). Depression in patients with Huntington disease correlates with alterations of the brain stem raphe depicted by transcranial sonography. *Journal of Psychiatry & Neuroscience : JPN*, *36*(3), 187–194. https://doi.org/10.1503/jpn.100067

Kruse, C., Maier, F., Spottke, A., Bach, J.-P., Bartels, C., Buerger, K., Fellgiebel, A., Fliessbach, K., Frölich, L., Hausner, L., Hellmich, M., Klöppel, S., Klostermann, A., Kornhuber, J., Laske, C., Peters, O., Priller, J., Richter-Schmidinger, T., Schneider, A., … Jessen, F. (2023). Apathy in patients with Alzheimer's disease is a cost-driving factor. *Alzheimer's & Dementia*, *19*(7), 2853–2864. https://doi.org/10.1002/alz.12915

Kumfor, F., Irish, M., Hodges, J. R., & Piguet, O. (2013). The orbitofrontal cortex is involved in emotional enhancement of memory: Evidence from the dementias. *Brain*, *136*(10), 2992–3003. https://doi.org/10.1093/brain/awt185

Kumfor, F., Zhen, A., Hodges, J. R., Piguet, O., & Irish, M. (2018). Apathy in Alzheimer's disease and frontotemporal dementia: Distinct clinical profiles and neural correlates. *Cortex*, *103*, 350–359. https://doi.org/10.1016/j.cortex.2018.03.019

Kurniawan, I. T., Guitart-Masip, M., & Dolan, R. J. (2011). Dopamine and effort-based decision making. *Frontiers in Neuroscience*, *5*. https://doi.org/10.3389/fnins.2011.00081

Kwon, J.-Y., Sawatzky, R., Baumbusch, J., Lauck, S., & Ratner, P. A. (2021). Growth mixture models: A case example of the longitudinal analysis of patient-reported outcomes data captured by a clinical registry. *BMC Medical Research Methodology*, *21*, 79. https://doi.org/10.1186/s12874-021-01276-z

Lafond-Brina, G., & Bonnefond, A. (2022). The stability of multidimensional subclinical apathy during a pandemic and its relations to psycho-behavioral factors. *Scientific Reports*, *12*(1), 2931. https://doi.org/10.1038/s41598-022-06777-5

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00863

Lanctôt, K. L., Agüera-Ortiz, L., Brodaty, H., Francis, P. T., Geda, Y. E., Ismail, Z., Marshall, G. A., Mortby, M. E., Onyike, C. U., Padala, P. R., Politis, A. M., Rosenberg, P. B., Siegel, E., Sultzer, D. L., & Abraham, E. H. (2017). Apathy associated with neurocognitive disorders: Recent progress and future directions. *Alzheimer's & Dementia*, *13*(1), 84–100. https://doi.org/10.1016/j.jalz.2016.05.008

Lanctôt, K. L., Ismail, Z., Bawa, K. K., Cummings, J. L., Husain, M., Mortby, M. E., & Robert, P. (2023). Distinguishing apathy from depression: A review differentiating the behavioral, neuroanatomic, and treatment-related aspects of apathy from depression in neurocognitive disorders. *International Journal of Geriatric Psychiatry*, *38*(2), e5882. https://doi.org/10.1002/gps.5882

Lanctôt, K. L., Moosa, S., Herrmann, N., Leibovitch, F. S., Rothenburg, L., Cotter, A., & Black, S. E. (2007). A SPECT study of apathy in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *24*(1), 65–72. https://doi.org/10.1159/000103633

Lanctôt, K. L., Scherer, R. W., Li, A., Vieira, D., Coulibaly, H., Rosenberg, P. B., Herrmann, N., Lerner, A. J., Padala, P. R., Brawman-Mintzer, O., Van Dyck, C. H., Porsteinsson, A. P., Craft, S., Levey, A., Burke, W. J., & Mintzer, J. E. (2021). Measuring apathy in Alzheimer's disease in the Apathy in Dementia Methylphenidate Trial 2 (ADMET 2): A comparison of instruments. *The American Journal of Geriatric Psychiatry*, *29*(1), 81–89. https://doi.org/10.1016/j.jagp.2020.05.020

Landes, A. M., Sperry, S. D., & Strauss, M. E. (2005). Prevalence of apathy, dysphoria, and depression in relation to dementia severity in Alzheimer's disease. *The Journal of*

Neuropsychiatry and Clinical Neurosciences, *17*(3), 342–349. https://doi.org/10.1176/jnp.17.3.342

Landes, A. M., Sperry, S. D., Strauss, M. E., & Geldmacher, D. S. (2001). Apathy in Alzheimer's disease. *Journal of the American Geriatrics Society*, *49*(12), 1700–1707. https://doi.org/10.1046/j.1532-5415.2001.49282.x

Landwehrmeyer, G. B., Fitzer-Attas, C. J., Giuliano, J. D., Gonçalves, N., Anderson, K. E., Cardoso, F., Ferreira, J. J., Mestre, T. A., Stout, J. C., & Sampaio, C. (2016). Data analytics from Enroll-HD, a global clinical research platform for Huntington's disease. *Movement Disorders Clinical Practice*, *4*(2), 212–224. https://doi.org/10.1002/mdc3.12388

Langbehn, D. R., Hayden, M., & Paulsen, J. S. (2010). CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, *153B*(2), 397–408. https://doi.org/10.1002/ajmg.b.30992

Laplane, D., & Degos, J. D. (1983). Motor neglect. *Journal of Neurology, Neurosurgery & Psychiatry*, *46*(2), 152–158. https://doi.org/10.1136/jnnp.46.2.152

Lavretsky, H., Zheng, L., Weiner, M. W., Mungas, D., Reed, B., Kramer, J. H., Jagust, W., Chui, H., & Mack, W. J. (2008). The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *International Journal of Geriatric Psychiatry*, *23*(10), 1040–1050. https://doi.org/10.1002/gps.2030

Le Heron, C., Apps., M. A. J., & Husain, M. (2018). The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia*, *118*, 54–67. https://doi.org/10.1016/j.neuropsychologia.2017.07.003

Le Heron, C., Holroyd, C. B., Salamone, J., & Husain, M. (2019). Brain mechanisms underlying apathy. *Journal of Neurology, Neurosurgery & Psychiatry*, *90*(3), 302–312. https://doi.org/10.1136/jnnp-2018-318265

Le Heron, C., Manohar, S., Plant, O., Muhammed, K., Griffanti, L., Nemeth, A., Douaud, G., Markus, H. S., & Husain, M. (2018). Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. *Brain*. https://doi.org/10.1093/brain/awy257

Lechowski, L., Benoit, M., Chassagne, P., Vedel, I., Tortrat, D., Teillet, L., & Vellas, B. (2009). Persistent apathy in Alzheimer's disease as an independent factor of rapid functional decline: The REAL longitudinal cohort study. *International Journal of Geriatric Psychiatry*, *24*(4), 341–346. https://doi.org/10.1002/gps.2125

Lee, J.-M., Ramos, E. M., Lee, J.-H., Gillis, T., Mysore, J. S., Hayden, M. R., Warby, S. C., Morrison, P., Nance, M., Ross, C. A., Margolis, R. L., Squitieri, F., Orobello, S., Di Donato, S., Gomez-Tortosa, E., Ayuso, C., Suchowersky, O., Trent, R. J. A., McCusker, E., … Zauber, E. (2012). CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. *Neurology*, *78*(10), 690–695. https://doi.org/10.1212/WNL.0b013e318249f683

Leemans, A., & Jones, D. K. (2009). The B-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine*, *61*(6), 1336–1349. https://doi.org/10.1002/mrm.21890

Leentjens, A. F. G., Dujardin, K., Marsh, L., Martinez-Martin, P., Richard, I. H., Starkstein, S. E., Weintraub, D., Sampaio, C., Poewe, W., Rascol, O., Stebbins, G. T., & Goetz, C. G. (2008). Apathy and anhedonia rating scales in Parkinson's disease: Critique and recommendations. *Movement Disorders*, *23*(14), 2004–2014. https://doi.org/10.1002/mds.22229

Leh, S. E., Petrides, M., & Strafella, A. P. (2010). The neural circuitry of executive functions in healthy subjects and Parkinson's disease. *Neuropsychopharmacology*, *35*(1), 70–85. https://doi.org/10.1038/npp.2009.88

Leh, S. E., Ptito, A., Chakravarty, M. M., & Strafella, A. P. (2007). Fronto-striatal connections in the human brain: A probabilistic diffusion tractography study. *Neuroscience Letters*, *419*(2), 113–118. https://doi.org/10.1016/j.neulet.2007.04.049

Levy, M. L., Cummings, J. L., Fairbanks, L. A., Masterman, D., Miller, B. L., Craig, A. H., Paulsen, J. S., & Litvan, I. (1998). Apathy is not depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 314–319.

Levy, R. (2012). Apathy: A pathology of goal-directed behaviour. A new concept of the clinic and pathophysiology of apathy. *Revue Neurologique*, *168*(8–9), 585–597. https://doi.org/10.1016/j.neurol.2012.05.003

Levy, R. (2021). Apathy: A pathology of goal-directed behaviour and prefrontal cortex-basal ganglia circuits. In K. L. Lanctôt & A. Aleman (Eds.), *Apathy: Clinical and Neuroscientific Perspectives from Neurology and Psychiatry* (pp. 156–173). Oxford University Press.

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. *Cerebral Cortex*, *16*(7), 916–928. https://doi.org/10.1093/cercor/bhj043

Lhermitte, F., Pillon, B., & Serdaru, M. (1986). Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: A neuropsychological study of 75 patients. *Annals of Neurology*, *19*(4), 326–334. https://doi.org/10.1002/ana.410190404

Ligthart, S. A., Richard, E., Fransen, N. L., Eurelings, L. S. M., Beem, L., Eikelenboom, P., van Gool, W. A., & Moll van Charante, E. P. (2012). Association of vascular factors with apathy in community-dwelling elderly individuals. *Archives of General Psychiatry*, *69*(6), 636–642. https://doi.org/10.1001/archgenpsychiatry.2011.1858

Litvan, I., Paulsen, J. S., Mega, M. S., & Cummings, J. L. (1998). Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. *Archives of Neurology*, *55*(10), 1313–1319. https://doi.org/10.1001/archneur.55.10.1313

Liu, A. M., Koppel, E., & Anderson, K. E. (2023). Understanding the relationship between perseveration, comorbid behavioral symptoms, motor decline, functional decline, and self-report accuracy in Huntington disease can help inform clinical practice. *Cognitive and Behavioral Neurology*, *36*(2), 93–99. https://doi.org/10.1097/WNN.0000000000000331

Lockwood, P. L., Ang, Y.-S., Husain, M., & Crockett, M. J. (2017). Individual differences in empathy are associated with apathy-motivation. *Scientific Reports*, *7*(1), 17293. https://doi.org/10.1038/s41598-017-17415-w

Lohner, V., Brookes, R. L., Hollocks, M. J., Morris, R. G., & Markus, H. S. (2017). Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. *PLOS ONE*, *12*(5), e0176943. https://doi.org/10.1371/journal.pone.0176943

Long, J. (2011). *Longitudinal data analysis for the behavioral sciences using R*. Sage Publications, Inc.

Lüdecke, D., Makowski, D., & Waggoner, P. (2019). *Performance: Assessment of regression models performance*. https://easystats.github.io/performance/

Lueken, U., Seidl, U., Völker, L., Schweiger, E., Kruse, A., & Schröder, J. (2007). Development of a short version of the Apathy Evaluation Scale specifically adapted for demented nursing home residents. *The American Journal of Geriatric Psychiatry*, *15*(5), 376–385. https://doi.org/10.1097/JGP.0b013e3180437db3

Luther, L., Firmin, R. L., Lysaker, P. H., Minor, K. S., & Salyers, M. P. (2018). A meta-analytic review of self-reported, clinician-rated, and performance-based motivation measures in schizophrenia: Are we measuring the same "stuff"? *Clinical Psychology Review*, *61*, 24–37. https://doi.org/10.1016/j.cpr.2018.04.001

MacDonald, M. E., Ambrose, C. M., Duyao, M. P., Myers, R. H., Lin, C., Srinidhi, L., Barnes, G., Taylor, S. A., James, M., Groot, N., MacFarlane, H., Jenkins, B., Anderson, M. A., Wexler, N. S., Gusella, J. F., Bates, G. P., Baxendale, S., Hummerich, H., Kirby, S., … Harper, P. S. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*, *72*(6), 971–983. https://doi.org/10.1016/0092-8674(93)90585-E

Maltby, J., Ovaska-Stafford, N., & Gunn, S. (2021). The structure of mental health symptoms in Huntington's disease: Comparisons with healthy populations. *Journal of Clinical and*

Experimental Neuropsychology, *43*(7), 737–752. https://doi.org/10.1080/13803395.2021.2002824

Manera, V., Fabre, R., Daumas, L., Zeghari, R., Derreumaux, A., Payne, M., Lemaire, J., Sacco, G., Gros, A., & Robert, P. (2023). Cutoff scores for the "Interest game", an application for the assessment of diminished interest in neurocognitive disorders. *Frontiers in Psychiatry*, *14*, 1126479. https://doi.org/10.3389/fpsyt.2023.1126479

Manohar, S. G., & Husain, M. (2016). Human ventromedial prefrontal lesions alter incentivisation by reward. *Cortex*, *76*, 104–120. https://doi.org/10.1016/j.cortex.2016.01.005

Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *NeuroImage*, *37*(2), 579–588. https://doi.org/10.1016/j.neuroimage.2007.05.019

Marin, R. S. (1991). Apathy: A neuropsychiatric syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *3*(3), 243–254. https://doi.org/10.1176/jnp.3.3.243

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research*, *38*, 143–162.

Marin, R. S., Firinciogullari, S., & Biedrzycki, R. C. (1993). The sources of convergence between measures of apathy and depression. *Journal of Affective Disorders*, *28*(1), 7–14. https://doi.org/10.1016/0165-0327(93)90072-R

Martínez-Corral, M., Pagonabarraga, J., Llebaria, G., Pascual-Sedano, B., García-Sánchez, C., Gironell, A., & Kulisevsky, J. (2010). Facial emotion recognition impairment in patients with Parkinson's disease and isolated apathy. *Parkinson's Disease*, *2010*, 930627. https://doi.org/10.4061/2010/930627

Martinez-Horta, S., Perez-Perez, J., Oltra-Cucarella, J., Sampedro, F., Horta-Barba, A., Puig-Davi, A., Pagonabarraga, J., & Kulisevsky, J. (2023). Divergent cognitive trajectories in early stage Huntington's disease: A 3-year longitudinal study. *European Journal of Neurology*, *30*(7), 1871–1879. https://doi.org/10.1111/ene.15806

Martinez-Horta, S., Perez-Perez, J., Sampedro, F., Pagonabarraga, J., Horta-Barba, A., Carceller-Sindreu, M., Gomez-Anson, B., Lozano-Martinez, G. A., Lopez-Mora, D. A., Camacho, V., Fernández-León, A., Carrió, I., & Kulisevsky, J. (2018). Structural and metabolic brain correlates of apathy in Huntington's disease. *Movement Disorders*, *33*(7), 1151–1159. https://doi.org/10.1002/mds.27395

Martinez-Horta, S., Perez-Perez, J., van Duijn, E., Fernandez-Bobadilla, R., Carceller, M., Pagonabarraga, J., Pascual-Sedano, B., Campolongo, A., Ruiz-Idiago, J., Sampedro, F., Landwehrmeyer, G. B., & Kulisevsky, J. (2016). Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. *Parkinsonism & Related Disorders*, *25*, 58–64. https://doi.org/10.1016/j.parkreldis.2016.02.008

Martinez-Horta, S., Sampedro, F., Pagonabarraga, J., Fernandez-Bobadilla, R., Marin-Lahoz, J., Riba, J., & Kulisevsky, J. (2017). Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. *Brain Imaging and Behavior*, *11*(5), 1334–1342. https://doi.org/10.1007/s11682-016-9607-5

Mason, S., & Barker, R. (2016). Advancing pharmacotherapy for treating Huntington's disease: A review of the existing literature. *Expert Opinion on Pharmacotherapy*, *17*(1), 41–52. https://doi.org/10.1517/14656566.2016.1109630

Mason, S., & Barker, R. A. (2015). Rating apathy in Huntington's disease: Patients and companions agree. *Journal of Huntington's Disease*, *4*, 49–59. https://doi.org/10.3233/JHD-140133

Massey, T. H., & McLauchlan, D. J. (2024). Huntington's disease: A clinical primer for acute and general physicians. *Clinical Medicine*, *24*(2), 100200. https://doi.org/10.1016/j.clinme.2024.100200

Massimo, L., Evans, L. K., & Grossman, M. (2014). Differentiating subtypes of apathy to improve person-centered care in frontotemporal degeneration. *Journal of Gerontological Nursing*, *40*(10), 58–65. https://doi.org/10.3928/00989134-20140827-01

Massimo, L., Powers, C., Moore, P., Vesely, L., Avants, B., Gee, J., Libon, D. J., & Grossman, M. (2009). Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration.

Dementia and Geriatric Cognitive Disorders, *27*(1), 96–104. https://doi.org/10.1159/000194658

Massimo, L., Powers, J. P., Evans, L. K., McMillan, C. T., Rascovsky, K., Eslinger, P., Ersek, M., Irwin, D. J., & Grossman, M. (2015). Apathy in frontotemporal degeneration: Neuroanatomical evidence of impaired goal-directed behavior. *Frontiers in Human Neuroscience*, *9*. https://doi.org/10.3389/fnhum.2015.00611

Matmati, J., Verny, C., & Allain, P. (2021). Apathy and Huntington's disease: A literature review based on PRISMA. *The Journal of Neuropsychiatry and Clinical Neurosciences*, appi.neuropsych.21060154. https://doi.org/10.1176/appi.neuropsych.21060154

Mayberg, H. S., Starkstein, S. E., Peyser, C. E., Brandt, J., Dannals, R. F., & Folstein, S. E. (1992). Paralimbic frontal lobe hypometabolism in depression associated with Huntington's disease. *Neurology*, *42*(9), 1791–1797. Scopus.

M'Barek, L., Radakovic, R., Noquet, M., Laurent, A., & Allain, P. (2020). Different aspects of emotional processes in apathy: Application of the French translated Dimensional Apathy Scale. *Current Psychology*, *39*(2), 564–570. https://doi.org/10.1007/s12144-017-9775-5

McAllister, B., Gusella, J. F., Landwehrmeyer, G. B., Lee, J.-M., MacDonald, M. E., Orth, M., Rosser, A. E., Williams, N. M., Holmans, P., Jones, L., Massey, T. H., & on behalf of the REGISTRY Investigators of the European Huntington's Disease Network. (2021). Timing and impact of psychiatric, cognitive, and motor abnormalities in Huntington disease. *Neurology*, *96*(19), e2395–e2406. https://doi.org/10.1212/WNL.0000000000011893

McArdle, J. J., Hamgami, F., Jones, K., Jolesz, F., Kikinis, R., Spiro, A., & Albert, M. S. (2004). Structural modeling of dynamic changes in memory and brain structure using longitudinal data from the normative aging study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *59*(6), P294–P304. https://doi.org/10.1093/geronb/59.6.P294

McColgan, P., Razi, A., Gregory, S., Seunarine, K. K., Durr, A., Roos, R. A. C., Leavitt, B. R., Scahill, R. I., Clark, C. A., Langbehn, D. R., Rees, G., Tabrizi, S. J., & Track On-HD Investigators. (2017). Structural and functional brain network correlates of depressive symptoms in

premanifest Huntington's disease. *Human Brain Mapping*, *38*(6), 2819–2829. https://doi.org/10.1002/hbm.23527

McColgan, P., Seunarine, K. K., Razi, A., Cole, J. H., Gregory, S., Durr, A., Roos, R. A. C., Stout, J. C., Landwehrmeyer, B., Scahill, R. I., Clark, C. A., Rees, G., Tabrizi, S. J., & Track-HD Investigators. (2015). Selective vulnerability of Rich Club brain regions is an organizational principle of structural connectivity loss in Huntington's disease. *Brain: A Journal of Neurology*, *138*(Pt 11), 3327–3344. https://doi.org/10.1093/brain/awv259

McColgan, P., & Tabrizi, S. J. (2018). Huntington's disease: A clinical review. *European Journal of Neurology*, *25*(1), 24–34. https://doi.org/10.1111/ene.13413

McLauchlan, D. J., Lancaster, T., Craufurd, D., Linden, D. E. J., & Rosser, A. E. (2019). Insensitivity to loss predicts apathy in Huntington's disease. *Movement Disorders*, mds.27787. https://doi.org/10.1002/mds.27787

McNally, G., Rickards, H., Horton, M., & Craufurd, D. (2015). Exploring the validity of the short version of the Problem Behaviours Assessment (PBA-s) for Huntington's disease: A Rasch analysis. *Journal of Huntington's Disease*, *4*(4), 347–369.

McPherson, S., Fairbanks, L., Tiken, S., Cummings, J. L., & Back-Madruga, C. (2002). Apathy and executive function in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *8*(3), 373–381. https://doi.org/10.1017/S1355617702813182

Mechelli, A., Friston, K. J., Frackowiak, R. S. J., & Price, C. J. (2005). Structural covariance in the human cortex. *Journal of Neuroscience*, *25*(36), 8303–8310. https://doi.org/10.1523/JNEUROSCI.0357-05.2005

Mega, M. S., & Cummings, J. L. (1994). Frontal-subcortical circuits and neuropsychiatric disorders. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *6*(4), 358–370. https://doi.org/10.1176/jnp.6.4.358

Mega, M. S., Cummings, J. L., Salloway, S., & Malloy, P. (1997). The limbic system: An anatomic, phylogenetic, and clinical perspective. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *9*(3), 315–330. https://doi.org/10.1176/jnp.9.3.315

Mendez, M. F., Adams, N. L., & Lewandowski, K. S. (1989). Neurobehavioral changes associated with caudate lesions. *Neurology*, *39*(3), 349–349. https://doi.org/10.1212/WNL.39.3.349

Mendez, M. F., Lauterbach, E. C., Sampson, S. M., & ANPA Committee on Research. (2008). An evidence-based review of the psychopathology of frontotemporal dementia: A report of the ANPA Committee on Research. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *20*(2), 130–149. https://doi.org/10.1176/jnp.2008.20.2.130

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*(5), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mestre, T. A., Duijn, E. van, Davis, A. M., Bachoud-Lévi, A.-C., Busse, M., Anderson, K. E., Ferreira, J. J., Mahlknecht, P., Tumas, V., Sampaio, C., Goetz, C. G., Cubo, E., Stebbins, G. T., & Martinez-Martin, P. (2016). Rating scales for behavioral symptoms in Huntington's disease: Critique and recommendations. *Movement Disorders*, *31*(10), 1466–1478. https://doi.org/10.1002/mds.26675

Meyer, A., Zimmermann, R., Gschwandtner, U., Hatz, F., Bousleiman, H., Schwarz, N., & Fuhr, P. (2015). Apathy in Parkinson's disease is related to executive function, gender and age but not to depression. *Frontiers in Aging Neuroscience*, *6*. https://doi.org/10.3389/fnagi.2014.00350

Migliore, S., D'Aurizio, G., Maffi, S., Ceccarelli, C., Ristori, G., Romano, S., Castaldo, A., Mariotti, C., Curcio, G., & Squitieri, F. (2021). Cognitive and behavioral associated changes in manifest Huntington disease: A retrospective cross-sectional study. *Brain and Behavior*, *11*(7), e02151. https://doi.org/10.1002/brb3.2151

Miller, D. S., Robert, P., Ereshefsky, L., Adler, L., Bateman, D., Cummings, J., DeKosky, S. T., Fischer, C. E., Husain, M., Ismail, Z., Jaeger, J., Lerner, A. J., Li, A., Lyketsos, C. G., Manera, V., Mintzer, J., Moebius, H. J., Mortby, M., Meulien, D., … Lanctôt, K. L. (2021). Diagnostic criteria for apathy in neurocognitive disorders. *Alzheimer's & Dementia*, *17*(12), 1892–1904. https://doi.org/10.1002/alz.12358

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Misiura, M. B., Ciarochi, J., Vaidya, J., Bockholt, J., Johnson, H. J., Calhoun, V. D., Paulsen, J. S., Turner, J. A., & the PREDICT-HD Investigators and Working Group. (2019). Apathy is related to cognitive control and striatum volumes in prodromal Huntington's disease. *Journal of the International Neuropsychological Society*, 1–8. https://doi.org/10.1017/S1355617719000067

Mito, R., Raffelt, D., Dhollander, T., Vaughan, D. N., Tournier, J.-D., Salvado, O., Brodtmann, A., Rowe, C. C., Villemagne, V. L., & Connelly, A. (2018). Fibre-specific white matter reductions in Alzheimer's disease and mild cognitive impairment. *Brain*, *141*(3), 888–902. https://doi.org/10.1093/brain/awx355

Mogenson, G., Jones, D., & Yim, C. (1980). From motivation to action: Functional interface between the limbic system and the motor system. *Progress in Neurobiology*, *14*(2–3), 69–97. https://doi.org/10.1016/0301-0082(80)90018-0

Mograbi, D. C., & Morris, R. G. (2014). On the relation among mood, apathy, and anosognosia in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *20*(1), 2–7. https://doi.org/10.1017/S1355617713001276

Mohammad, D., Ellis, C., Rau, A., Rosenberg, P. B., Mintzer, J., Ruthirakuhan, M., Herrmann, N., & Lanctôt, K. L. (2018). Psychometric properties of Apathy Scales in dementia: A systematic review. *Journal of Alzheimer's Disease*, *66*(3), 1065–1082. https://doi.org/10.3233/JAD-180485

Mohan, A., Sun, Z., Ghosh, S., Li, Y., Sathe, S., Hu, J., & Sampaio, C. (2022). A machine-learning derived Huntington's disease progression model: Insights for clinical trial design. *Movement Disorders*, *37*(3), 553–562. https://doi.org/10.1002/mds.28866

Monchi, O., Petrides, M., Strafella, A. P., Worsley, K. J., & Doyon, J. (2006). Functional role of the basal ganglia in the planning and execution of actions. *Annals of Neurology*, *59*(2), 257–264. https://doi.org/10.1002/ana.20742

Montoya-Murillo, G., Ibarretxe-Bilbao, N., Peña, J., & Ojeda, N. (2019). The impact of apathy on cognitive performance in the elderly. *International Journal of Geriatric Psychiatry*, *34*(5), 657–665. https://doi.org/10.1002/gps.5062

Moreau, C., Delval, A., Defebvre, L., Dujardin, K., Duhamel, A., Petyt, G., Vuillaume, I., Corvol, J.-C., Brefel-Courbon, C., Ory-Magne, F., Guehl, D., Eusebio, A., Fraix, V., Saulnier, P.-J., Lagha-Boukbiza, O., Durif, F., Faighel, M., Giordana, C., Drapier, S., … Devos, D. (2012). Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: A multicentre, parallel, randomised, placebo-controlled trial. *The Lancet Neurology*, *11*(7), 589–596. https://doi.org/10.1016/S1474-4422(12)70106-0

Moretti, R., & Signori, R. (2016). Neural correlates for apathy: Frontal-prefrontal and parietal cortical-subcortical circuits. *Frontiers in Aging Neuroscience*, *8*. https://doi.org/10.3389/fnagi.2016.00289

Morris, L. S., Kundu, P., Dowell, N., Mechelmans, D. J., Favre, P., Irvine, M. A., Robbins, T. W., Daw, N., Bullmore, E. T., Harrison, N. A., & Voon, V. (2016). Fronto-striatal organization: Defining functional and microstructural substrates of behavioural flexibility. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *74*, 118–133. https://doi.org/10.1016/j.cortex.2015.11.004

Mulin, E., Leone, E., Dujardin, K., Delliaux, M., Leentjens, A., Nobili, F., Dessi, B., Tible, O., Agüera-Ortiz, L., Osorio, R. S., Yessavage, J., Dachevsky, D., Verhey, F. Rj., Jentoft, A. J. C., Blanc, O., Llorca, P. M., & Robert, P. H. (2011). Diagnostic criteria for apathy in clinical practice. *International Journal of Geriatric Psychiatry*, *26*(2), 158–165. https://doi.org/10.1002/gps.2508

Muller, M. (2007). Dynamic time warping. In *Information Retrieval for Music and Motion* (pp. 69–84). Springer. https://doi.org/10.1007/978-3-540-74048-3_4

Muller, U., Czymmek, J., Thöne-Otto, A., & Yves Von Cramon, D. (2006). Reduced daytime activity in patients with acquired brain damage and apathy: A study with ambulatory actigraphy. *Brain Injury*, *20*(2), 157–160. https://doi.org/10.1080/02699050500443467

Naarding, P., Janzing, J. G., Eling, P., van der Werf, S., & Kremer, B. (2009). Apathy is not depression in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *21*(3), 266–270.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, *9*(11), nrn2478. https://doi.org/10.1038/nrn2478

Nair, A., Razi, A., Gregory, S., Rutledge, R. B., Rees, G., & Tabrizi, S. J. (2022). Imbalanced basal ganglia connectivity is associated with motor deficits and apathy in Huntington's disease. *Brain*, *145*(3), 991–1000. https://doi.org/10.1093/brain/awab367

Namkung, H., Kim, S.-H., & Sawa, A. (2017). The insula: An underestimated brain area in clinical neuroscience, psychiatry, and neurology. *Trends in Neurosciences*, *40*(4), 200–207. https://doi.org/10.1016/j.tins.2017.02.002

Narme, P., Mouras, H., Roussel, M., Devendeville, A., & Godefroy, O. (2013). Assessment of socioemotional processes facilitates the distinction between frontotemporal lobar degeneration and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *35*(7), 728–744. https://doi.org/10.1080/13803395.2013.823911

Németh, G., Hegedüs, K., & Molnâr, L. (1988). Akinetic mutism associated with bicingular lesions: Clinicopathological and functional anatomical correlates. *European Archives of Psychiatry and Neurological Sciences*, *237*(4), 218–222. https://doi.org/10.1007/BF00449910

Niccolini, F., & Politis, M. (2014). Neuroimaging in Huntington's disease. *World Journal of Radiology*, *6*(6), 301–312. https://doi.org/10.4329/wjr.v6.i6.301

Nimmagadda, S. R., Agrawal, N., Worrall-Davies, A., Markova, I., & Rickards, H. (2011). Determinants of irritability in Huntington's disease. *Acta Neuropsychiatrica*, *23*(6), 309–314. https://doi.org/10.1111/j.1601-5215.2011.00563.x

Njomboro, P., & Deb, S. (2014). Distinct neuropsychological correlates of cognitive, behavioral, and affective apathy sub-domains in acquired brain injury. *Frontiers in Neurology*, *5*. https://doi.org/10.3389/fneur.2014.00073

Nobis, L., & Husain, M. (2018). Apathy in Alzheimer's disease. *Current Opinion in Behavioral Sciences*, *22*, 7–13. https://doi.org/10.1016/j.cobeha.2017.12.007

Novak, M. J. U., & Tabrizi, S. J. (2010). Huntington's disease. *BMJ*, *340*(jun30 4), c3109–c3109. https://doi.org/10.1136/bmj.c3109

Nugent, A. C., Luckenbaugh, D. A., Wood, S. E., Bogers, W., Zarate, C. A., & Drevets, W. C. (2013). Automated subcortical segmentation using FIRST: Test-retest reliability, inter-scanner reliability, and comparison to manual segmentation. *Human Brain Mapping*, *34*(9), 2313–2329. https://doi.org/10.1002/hbm.22068

Odish, O. F. F., Leemans, A., Reijntjes, R. H. A. M., van den Bogaard, S. J. A., Dumas, E. M., Wolterbeek, R., Tax, C. M. W., Kuijf, H. J., Vincken, K. L., van der Grond, J., & Roos, R. A. C. (2015). Microstructural brain abnormalities in Huntington's disease: A two-year follow-up. *Human Brain Mapping*, *36*(6), 2061–2074. https://doi.org/10.1002/hbm.22756

Onoda, K., & Yamaguchi, S. (2015). Dissociative contributions of the anterior cingulate cortex to apathy and depression: Topological evidence from resting-state functional MRI. *Neuropsychologia*, *77*, 10–18. https://doi.org/10.1016/j.neuropsychologia.2015.07.030

Oosterloo, M., Craufurd, D., Nijsten, H., & Van Duijn, E. (2019). Obsessive-compulsive and perseverative behaviors in Huntington's disease. *Journal of Huntington's Disease*, *8*(1), 1–7. https://doi.org/10.3233/JHD-180335

Osborne-Crowley, K., Andrews, S. C., Labuschagne, I., Nair, A., Scahill, R., Craufurd, D., Tabrizi, S. J., Stout, J. C., & the TRACK-HD Investigators. (2019). Apathy associated with impaired recognition of happy facial expressions in Huntington's disease. *Journal of the International Neuropsychological Society*, *25*(05), 453–461. https://doi.org/10.1017/S1355617718001224

Padala, P. R., Burke, W. J., Bhatia, S. C., & Petty, F. (2007). Treatment of apathy with methylphenidate. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(1), 81–83. https://doi.org/10.1176/jnp.2007.19.1.81

Pagonabarraga, J., Kulisevsky, J., Strafella, A. P., & Krack, P. (2015). Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology*, *14*(5), 518–531.

Paoli, R., Botturi, A., Ciammola, A., Silani, V., Prunas, C., Lucchiari, C., Zugno, E., & Caletti, E. (2017). Neuropsychiatric burden in Huntington's disease. *Brain Sciences*, *7*(6), 67. https://doi.org/10.3390/brainsci7060067

Pardini, M., Cordano, C., Guida, S., Grafman, J., Krueger, F., Sassos, D., Massucco, D., Abate, L., Yaldizli, Ö., Serrati, C., Amore, M., Mattei, C., Cocito, L., & Emberti Gialloreti, L. (2016). Prevalence and cognitive underpinnings of isolated apathy in young healthy subjects. *Journal of Affective Disorders*, *189*, 272–275. https://doi.org/10.1016/j.jad.2015.09.062

Parrotta, I., Cacciatore, S., D'Andrea, F., D'Anna, M., Giancaterino, G., Lazzaro, G., Arcara, G., & Manzo, N. (2024). Prevalence, treatment, and neural correlates of apathy in different forms of dementia: A narrative review. *Neurological Sciences*, *45*(4), 1343–1376. https://doi.org/10.1007/s10072-023-07197-7

Passamonti, L., Lansdall, C., & Rowe, J. (2018). The neuroanatomical and neurochemical basis of apathy and impulsivity in frontotemporal lobar degeneration. *Current Opinion in Behavioral Sciences*, *22*, 14–20. https://doi.org/10.1016/j.cobeha.2017.12.015

Paulsen, J. S., Langbehn, D. R., Stout, J. C., Aylward, E., Ross, C. A., Nance, M., Guttman, M., Johnson, S., MacDonald, M., Beglinger, L. J., Duff, K., Kayson, E., Biglan, K., Shoulson, I., Oakes, D., Hayden, M., & The Predict-HD Investigators and Coordinators of the Huntington Study Group. (2008). Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(8), 874–880. https://doi.org/10.1136/jnnp.2007.128728

Paulsen, J. S., Long, J. D., Johnson, H. J., Aylward, E. H., Ross, C. A., Williams, J. K., Nance, M. A., Erwin, C. J., Westervelt, H. K., Harrington, D. L., Bockholt, H. J., Zhang, Y., McCusker, E. A., Chiu, E. M., & Panegyres, P. K. (2014). Clinical and biomarker changes in premanifest Huntington disease show trial feasibility: A decade of the PREDICT-HD study. *Frontiers in Aging Neuroscience*, *6*. https://doi.org/10.3389/fnagi.2014.00078

Paulsen, J. S., Miller, A. C., Hayes, T., & Shaw, E. (2017). Chapter 6—Cognitive and behavioral changes in Huntington disease before diagnosis. In A. S. Feigin & K. E. Anderson (Eds.), *Handbook of Clinical Neurology* (Vol. 144, pp. 69–91). Elsevier. https://doi.org/10.1016/B978-0-12-801893-4.00006-7

Paulsen, J. S., Nehl, C., Hoth, K. F., Kanz, J. E., Benjamin, M., Conybeare, R., McDowell, B., Turner, B., & The Huntington Study Group. (2005). Depression and stages of Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(4), 496–502. https://doi.org/10.1001/jama.1992.03490110111047

Paulsen, J. S., Nopoulos, P. C., Aylward, E., Ross, C. A., Johnson, H., Magnotta, V. A., Juhl, A., Pierson, R. K., Mills, J., Langbehn, D., & Nance, M. (2010). Striatal and white matter predictors of estimated diagnosis for Huntington disease. *Brain Research Bulletin*, *82*(3–4), 201–207. https://doi.org/10.1016/j.brainresbull.2010.04.003

Paulsen, J. S., Ready, R. E., Hamilton, J. M., Mega, M. S., & Cummings, J. L. (2001). Neuropsychiatric aspects of Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *71*(3), 310–314.

Pedersen, K. F., Larsen, J. P., & Aarsland, D. (2008). Validation of the Unified Parkinson's Disease Rating Scale (UPDRS) section I as a screening and diagnostic instrument for apathy in patients with Parkinson's disease. *Parkinsonism & Related Disorders*, *14*(3), 183–186. https://doi.org/10.1016/j.parkreldis.2007.07.015

Penney, J. B., Vonsattel, J. P., MacDonald, M. E., Gusella, J. F., & Myers, R. H. (1997). CAG repeat number governs the development rate of pathology in Huntington's disease. *Annals of Neurology*, *41*(5), 689–692. https://doi.org/10.1002/ana.410410521

Perri, R., Turchetta, C. S., Caruso, G., Fadda, L., Caltagirone, C., & Carlesimo, G. A. (2018). Neuropsychological correlates of cognitive, emotional-affective and auto-activation apathy in Alzheimer's disease. *Neuropsychologia*, *118*, 12–21. https://doi.org/10.1016/j.neuropsychologia.2018.01.039

Pessiglione, M., Schmidt, L., Draganski, B., Kalisch, R., Lau, H., Dolan, R. J., & Frith, C. D. (2007). How the brain translates money into force: A neuroimaging study of subliminal motivation. *Science*, *316*(5826), 904–906. https://doi.org/10.1126/science.1140459

Pessiglione, M., Vinckier, F., Bouret, S., Daunizeau, J., & Le Bouc, R. (2018). Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain: A Journal of Neurology*, *141*(3), 629–650. https://doi.org/10.1093/brain/awx278

Peters, F., Perani, D., Herholz, K., Holthoff, V., Beuthien-Baumann, B., Sorbi, S., Pupi, A., Degueldre, C., Lemaire, C., Collette, F., & Salmon, E. (2006). Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, *21*(5–6), 373–379. https://doi.org/10.1159/000091898

Petrides, M., & Pandya, D. N. (1999). Dorsolateral prefrontal cortex: Comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience*, *11*(3), 1011–1036. https://doi.org/10.1046/j.1460-9568.1999.00518.x

Philpott, A. L., Andrews, S. C., Staios, M., Churchyard, A., & Fisher, F. (2016). Emotion evaluation and social inference impairments in Huntington's disease. *Journal of Huntington's Disease*, *5*(2), 175–183. https://doi.org/10.3233/JHD-160190

Poletti, B., Solca, F., Maffi, S., Torre, S., Carelli, L., Aiello, E. N., Ferrucci, R., Priori, A., Monti, A., Verde, F., Ticozzi, N., Migliore, S., Scaricamazza, E., Casella, M., Squitieri, F., Ciammola, A., & Silani, V. (2022). Semiology and determinants of apathy across neurodegenerative motor disorders: A comparison between amyotrophic lateral sclerosis, Parkinson's and Huntington's disease. *Frontiers in Aging Neuroscience*, *14*, 1031908. https://doi.org/10.3389/fnagi.2022.1031908

Porcelli, S., Van Der Wee, N., Van Der Werff, S., Aghajani, M., Glennon, J. C., Van Heukelum, S., Mogavero, F., Lobo, A., Olivera, F. J., Lobo, E., Posadas, M., Dukart, J., Kozak, R., Arce, E., Ikram, A., Vorstman, J., Bilderbeck, A., Saris, I., Kas, M. J., & Serretti, A. (2019). Social brain, social dysfunction and social withdrawal. *Neuroscience & Biobehavioral Reviews*, *97*, 10–33. https://doi.org/10.1016/j.neubiorev.2018.09.012

Potter, N. T., Spector, E. B., & Prior, T. W. (2004). Technical standards and guidelines for Huntington disease testing. *Genetics in Medicine*, *6*(1), 61–65. https://doi.org/10.1097/01.GIM.0000106165.74751.15

Powers, J. P., Massimo, L., McMillan, C. T., Yushkevich, P. A., Zhang, H., Gee, J. C., & Grossman, M. (2014). White matter disease contributes to apathy and disinhibition in behavioral variant frontotemporal dementia. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, *27*(4), 206–214. https://doi.org/10.1097/WNN.0000000000000044

Prange, S., Metereau, E., Maillet, A., Lhommée, E., Klinger, H., Pelissier, P., Ibarrola, D., Heckemann, R. A., Castrioto, A., Tremblay, L., Sgambato, V., Broussolle, E., Krack, P., & Thobois, S. (2019). Early limbic microstructural alterations in apathy and depression in de novo Parkinson's disease. *Movement Disorders*, *34*(11), 1644–1654. https://doi.org/10.1002/mds.27793

Prange, S., Pagonabarraga, J., Krack, P., Kulisevsky, J., Sgambato, V., Tremblay, L., Thobois, S., & Broussolle, E. (2018). Historical crossroads in the conceptual delineation of apathy in Parkinson's disease. *Brain*, *141*(2), 613–619. https://doi.org/10.1093/brain/awx362

Quang, H., Wong, S., Husain, M., Piguet, O., Hodges, J. R., Irish, M., & Kumfor, F. (2021). Beyond language impairment: Profiles of apathy in primary progressive aphasia. *Cortex*, *139*, 73–85. https://doi.org/10.1016/j.cortex.2021.02.028

Quaranta, D., Marra, C., Rossi, C., Gainotti, G., & Masullo, C. (2012). Different apathy profile in behavioral variant of frontotemporal dementia and Alzheimer's disease: A preliminary investigation. *Current Gerontology and Geriatrics Research*, *2012*. https://doi.org/10.1155/2012/719250

Radakovic, R., & Abrahams, S. (2014). Developing a new apathy measurement scale: Dimensional Apathy Scale. *Psychiatry Research*, *219*(3), 658–663. https://doi.org/10.1016/j.psychres.2014.06.010

Radakovic, R., & Abrahams, S. (2018). Multidimensional apathy: Evidence from neurodegenerative disease. *Current Opinion in Behavioral Sciences*, *22*, 42–49. https://doi.org/10.1016/j.cobeha.2017.12.022

Radakovic, R., Davenport, R., Starr, J. M., & Abrahams, S. (2018). Apathy dimensions in Parkinson's disease. *International Journal of Geriatric Psychiatry*, *33*(1), 151–158. https://doi.org/10.1002/gps.4697

Radakovic, R., Gray, D., Dudley, K., Mioshi, E., Dick, D., Melchiorre, G., Gordon, H., Newton, J., Colville, S., Pal, S., Chandran, S., & Abrahams, S. (2020). Reliability and validity of the brief Dimensional Apathy Scale. *Archives of Clinical Neuropsychology*, *35*(5), 539–544. https://doi.org/10.1093/arclin/acaa002

Radakovic, R., Harley, C., Abrahams, S., & Starr, J. M. (2015). A systematic review of the validity and reliability of apathy scales in neurodegenerative conditions. *International Psychogeriatrics*, *27*(6), 903–923. https://doi.org/10.1017/S1041610214002221

Radakovic, R., McGrory, S., Chandran, S., Swingler, R., Pal, S., Stephenson, L., Colville, S., Newton, J., Starr, J. M., & Abrahams, S. (2020). The brief Dimensional Apathy Scale: A short clinical assessment of apathy. *The Clinical Neuropsychologist*, *34*(2), 423–435. https://doi.org/10.1080/13854046.2019.1621382

Radakovic, R., Starr, J. M., & Abrahams, S. (2017). A novel assessment and profiling of multidimensional apathy in Alzheimer's disease. *Journal of Alzheimer's Disease*, *60*(1), 57–67. https://doi.org/10.3233/JAD-170292

Radakovic, R., Stephenson, L., Colville, S., Swingler, R., Chandran, S., & Abrahams, S. (2016). Multidimensional apathy in ALS: Validation of the Dimensional Apathy Scale. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(6), 663–669. https://doi.org/10.1136/jnnp-2015-310772

Radakovic, R., Stephenson, L., Newton, J., Crockford, C., Swingler, R., Chandran, S., & Abrahams, S. (2017). Multidimensional apathy and executive dysfunction in amyotrophic lateral sclerosis. *Cortex*, *94*, 142–151. https://doi.org/10.1016/j.cortex.2017.06.023

Raimo, S., Trojano, L., Gaita, M., Spitaleri, D., & Santangelo, G. (2020). Assessing apathy in multiple sclerosis: Validation of the Dimensional Apathy Scale and comparison with Apathy Evaluation Scale. *Multiple Sclerosis and Related Disorders*, *38*, 101870. https://doi.org/10.1016/j.msard.2019.101870

Ranganathan, M., Kostyk, S. K., Allain, D. C., Race, J. A., & Daley, A. M. (2021). Age of onset and behavioral manifestations in Huntington's disease: An Enroll-HD cohort analysis. *Clinical Genetics*, *99*(1), 133–142. https://doi.org/10.1111/cge.13857

Raschka, T., Li, Z., Gaßner, H., Kohl, Z., Jukic, J., Marxreiter, F., & Fröhlich, H. (2024). Unraveling progression subtypes in people with Huntington's disease. *EPMA Journal*, *15*(2), 275–287. https://doi.org/10.1007/s13167-024-00368-2

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., Van Swieten, J. C., Seelaar, H., Dopper, E. G. P., Onyike, C. U., Hillis, A. E., Josephs, K. A., Boeve, B. F., Kertesz, A., Seeley, W. W., Rankin, K. P., Johnson, J. K., Gorno-Tempini, M.-L., Rosen, H., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(9), 2456–2477. https://doi.org/10.1093/brain/awr179

Ravina, B., Romer, M., Constantinescu, R., Biglan, K., Brocht, A., Kieburtz, K., Shoulson, I., & McDermott, M. P. (2008). The relationship between CAG repeat length and clinical progression in Huntington's disease. *Movement Disorders*, *23*(9), 1223–1227. https://doi.org/10.1002/mds.21988

Rawlins, M. D., Wexler, N. S., Wexler, A. R., Tabrizi, S. J., Douglas, I., Evans, S. J. W., & Smeeth, L. (2016). The prevalence of Huntington's Disease. *Neuroepidemiology*, *46*(2), 144–153. https://doi.org/10.1159/000443738

Ready, R. E., Mathews, M., Leserman, A., & Paulsen, J. S. (2008). Patient and caregiver quality of life in Huntington's disease. *Movement Disorders*, *23*(5), 721–726. https://doi.org/10.1002/mds.21920

Reedeker, N., Bouwens, J. A., Van Duijn, E., Giltay, E. J., Roos, R. A. C., & Van Der Mast, R. C. (2011). Incidence, course, and predictors of apathy in Huntington's disease: A two-year prospective study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(4), 434–441. https://doi.org/10.1176/jnp.23.4.jnp434

Reedeker, N., Van Der Mast, R. C., Giltay, E. J., Van Duijn, E., & Roos, R. A. C. (2010). Hypokinesia in Huntington's disease co-occurs with cognitive and global dysfunctioning. *Movement Disorders*, *25*(11), 1612–1618. https://doi.org/10.1002/mds.23136

Reijnders, J. S. A. M., Scholtissen, B., Weber, W. E. J., Aalten, P., Verhey, F. R. J., & Leentjens, A. F. G. (2010). Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging study using voxel-based morphometry. *Movement Disorders: Official Journal of the Movement Disorder Society*, *25*(14), 2318–2325. https://doi.org/10.1002/mds.23268

Reilmann, R., Leavitt, B. R., & Ross, C. A. (2014). Diagnostic criteria for Huntington's disease based on natural history. *Movement Disorders*, *29*(11), 1335–1341. https://doi.org/10.1002/mds.26011

Research Domain Criteria (RDoC)—National Institute of Mental Health (NIMH). (2024). https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc

Reyes, S., Viswanathan, A., Godin, O., Dufouil, C., Benisty, S., Hernandez, K., Kurtz, A., Jouvent, E., O'Sullivan, M., Czernecki, V., Bousser, M. G., Dichgans, M., & Chabriat, H. (2009). Apathy: A major symptom in CADASIL. *Neurology*, *72*(10), 905–910. https://doi.org/10.1212/01.wnl.0000344166.03470.f8

Rickards, H., De Souza, J., van Walsem, M., van Duijn, E., Simpson, S. A., Squitieri, F., Landwehrmeyer, B., & The European Huntington's Disease Network. (2011). Factor

analysis of behavioural symptoms in Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *82*(4), 411–412. https://doi.org/10.1136/jnnp.2009.181149

Riglin, L., Eyre, O., Thapar, A. K., Stringaris, A., Leibenluft, E., Pine, D. S., Tilling, K., Davey Smith, G., O'Donovan, M. C., & Thapar, A. (2019). Identifying novel types of irritability using a developmental genetic approach. *American Journal of Psychiatry*, *176*(8), 635–642. https://doi.org/10.1176/appi.ajp.2019.18101134

Riley, J. D., Moore, S., Cramer, S. C., & Lin, J. J. (2011). Caudate atrophy and impaired frontostriatal connections are linked to executive dysfunction in temporal lobe epilepsy. *Epilepsy & Behavior*, *21*(1), 80–87. https://doi.org/10.1016/j.yebeh.2011.03.013

Robert, G., Le Jeune, F., Dondaine, T., Drapier, S., Péron, J., Lozachmeur, C., Sauleau, P., Houvenaghel, J.-F., Travers, D., Millet, B., Vérin, M., & Drapier, D. (2014). Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: A PET study with conjunction analyses. *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(10), 1153–1158. https://doi.org/10.1136/jnnp-2013-307025

Robert, P. H., Clairet, S., Benoit, M., Koutaich, J., Bertogliati, C., Tible, O., Caci, H., Borg, M., Brocker, P., & Bedoucha, P. (2002). The Apathy Inventory: Assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *International Journal of Geriatric Psychiatry*, *17*(12), 1099–1105. https://doi.org/10.1002/gps.755

Robert, P. H., Darcourt, G., Koulibaly, M. P., Clairet, S., Benoit, M., Garcia, R., Dechaux, O., & Darcourt, J. (2006). Lack of initiative and interest in Alzheimer's disease: A single photon emission computed tomography study. *European Journal of Neurology*, *13*(7), 729–735. https://doi.org/10.1111/j.1468-1331.2006.01088.x

Robert, P. H., Lanctôt, K. L., Agüera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., Hanon, C., David, R., Dubois, B., Dujardin, K., Husain, M., König, A., Levy, R., Mantua, V., Meulien, D., Miller, D., Moebius, H. J., Rasmussen, J., Robert, G., … Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European Psychiatry*, *54*, 71–76. https://doi.org/10.1016/j.eurpsy.2018.07.008

Robert, P. H., & Manera, V. (2021). Chapter 1. Definition of apathy and differential diagnosis. In K. L. Lanctôt & A. Aleman (Eds.), *Apathy: Clinical and Neuroscientific Perspectives from Neurology and Psychiatry* (pp. 1–18). Oxford University Press.

Robert, P. H., Mulin, E., Malléa, P., & David, R. (2010). Apathy diagnosis, assessment, and treatment in Alzheimer's disease. *CNS Neuroscience & Therapeutics*, *16*(5), 263–271. https://doi.org/10.1111/j.1755-5949.2009.00132.x

Robert, P. H., Onyike, C. U., Leentjens, A. F. G., Dujardin, K., Aalten, P., Starkstein, S., Verhey, F. R. J., Yessavage, J., Clement, J. P., Drapier, D., Bayle, F., Benoit, M., Boyer, P., Lorca, P. M., Thibaut, F., Gauthier, S., Grossberg, G., Vellas, B., & Byrne, J. (2009). Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *European Psychiatry*, *24*(2), 98–104. https://doi.org/10.1016/j.eurpsy.2008.09.001

Robert, P. H., Zeghari, R., & Manera, V. (2019). Times are changing: Assessment of apathy using new technologies. *Alzheimer's & Dementia*, *15*, P161–P162. https://doi.org/10.1016/j.jalz.2019.06.4331

Robinson, G., Shallice, T., Bozzali, M., & Cipolotti, L. (2012). The differing roles of the frontal cortex in fluency tests. *Brain*, *135*(7), 2202–2214. https://doi.org/10.1093/brain/aws142

Robinson, J. L., Laird, A. R., Glahn, D. C., Blangero, J., Sanghera, M. K., Pessoa, L., Fox, P. M., Uecker, A., Friehs, G., Young, K. A., Griffin, J. L., Lovallo, W. R., & Fox, P. T. (2012). The functional connectivity of the human caudate: An application of meta-analytic connectivity modeling with behavioral filtering. *NeuroImage*, *60*(1), 117–129. https://doi.org/10.1016/j.neuroimage.2011.12.010

Rochat, L., Van der Linden, M., Renaud, O., Epiney, J.-B., Michel, P., Sztajzel, R., Spierer, L., & Annoni, J.-M. (2013). Poor reward sensitivity and apathy after stroke: Implication of basal ganglia. *Neurology*, *81*(19), 1674–1680. https://doi.org/10.1212/01.wnl.0000435290.49598.1d

Rogalsky, C., Vidal, C., Li, X., & Damasio, H. (2012). Risky decision-making in older adults without cognitive deficits: An fMRI study of VMPFC using the Iowa Gambling Task. *Social Neuroscience*, *7*(2), 178–190. https://doi.org/10.1080/17470919.2011.588340

Roos, R. A. (2010). Huntington's disease: A clinical review. *Orphanet Journal of Rare Diseases*, *5*(40), 1–8.

Rosas, H. D., Salat, D. H., Lee, S. Y., Zaleta, A. K., Pappu, V., Fischl, B., Greve, D., Hevelone, N., & Hersch, S. M. (2008). Cerebral cortex and the clinical expression of Huntington's disease: Complexity and heterogeneity. *Brain*, *131*(4), 1057–1068. https://doi.org/10.1093/brain/awn025

Rosen, H. J. (2011). Anosognosia in neurodegenerative disease. *Neurocase*, *17*(3), 231–241. https://doi.org/10.1080/13554794.2010.522588

Rosen, H. J., Hartikainen, K. M., Jagust, W., Kramer, J. H., Reed, B. R., Cummings, J. L., Boone, K., Ellis, W., Miller, C., & Miller, B. L. (2002). Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology*, *58*(11), 1608–1615. https://doi.org/10.1212/WNL.58.11.1608

Rosenblatt, A. (2007). Neuropsychiatry of Huntington's disease. *Dialogues in Clinical Neuroscience*, *9*(2), 191–197.

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology*, *10*(4), 204–216. https://doi.org/10.1038/nrneurol.2014.24

Ross, C. A., Reilmann, R., Cardoso, F., McCusker, E. A., Testa, C. M., Stout, J. C., Leavitt, B. R., Pei, Z., Landwehrmeyer, B., Martinez, A., Levey, J., Srajer, T., Bang, J., & Tabrizi, S. J. (2019). Movement Disorder Society task force viewpoint: Huntington's disease diagnostic categories. *Movement Disorders Clinical Practice*, *6*(7), 541–546. https://doi.org/10.1002/mdc3.12808

Ross, C. A., & Tabrizi, S. J. (2011). Huntington's disease: From molecular pathogenesis to clinical treatment. *The Lancet Neurology*, *10*(1), 83–98. https://doi.org/10.1016/S1474-4422(10)70245-3

Roth, R. M., Flashman, L. A., Saykin, A. J., McAllister, T. W., & Vidaver, R. (2004). Apathy in schizophrenia: Reduced frontal lobe volume and neuropsychological deficits. *The American Journal of Psychiatry*, *161*(1), 157–159. https://doi.org/10.1176/appi.ajp.161.1.157

Ruiz-Idiago, J. M., Floriach, M., Mareca, C., Salvador, R., López-Sendón, J. L., Mañanés, V., Cubo, E., Mariscal, N., Muñoz, E., Santacruz, P., Noguera, M. F., Vivancos, L., Roy, P., Pomarol-Clotet, E., Sarró, S., & on behalf of the Spanish Huntington Disease Network. (2017). Spanish validation of the Problem Behaviors Assessment–Short (PBA-s) for Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(1), 31–38. https://doi.org/10.1176/appi.neuropsych.16020025

Ruiz-Idiago, J. M., Pomarol-Clotet, E., & Salvador, R. (2023). Longitudinal analysis of neuropsychiatric symptoms in a large cohort of early-moderate manifest Huntington's disease patients. *Parkinsonism & Related Disorders*, *106*, 105228. https://doi.org/10.1016/j.parkreldis.2022.11.020

Rushworth, M. F. S., Behrens, T. E. J., Rudebeck, P. H., & Walton, M. E. (2007). Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends in Cognitive Sciences*, *11*(4), 168–176. https://doi.org/10.1016/j.tics.2007.01.004

Ruthirakuhan, M. T., Herrmann, N., Abraham, E. H., Chan, S., & Lanctôt, K. L. (2018). Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane Database of Systematic Reviews*, *2018*(6). https://doi.org/10.1002/14651858.CD012197.pub2

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: The DSM-5 approach. *Nature Reviews Neurology*, *10*(11), 634–643. https://doi.org/10.1038/nrneurol.2014.181

Salamone, J. D., Yohn, S. E., López-Cruz, L., San Miguel, N., & Correa, M. (2016). Activational and effort-related aspects of motivation: Neural mechanisms and implications for psychopathology. *Brain*, *139*(5), 1325–1347. https://doi.org/10.1093/brain/aww050

Sampedro, F., Martínez-Horta, S., Perez-Perez, J., Horta-Barba, A., Lopez-Mora, D. A., Camacho, V., Fernández-León, A., Gomez-Anson, B., Carrió, I., & Kulisevsky, J. (2019). Cortical atrophic-hypometabolic dissociation in the transition from premanifest to early-stage Huntington's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, *46*(5), 1111–1116. https://doi.org/10.1007/s00259-018-4257-z

Sampedro, F., Pérez-Pérez, J., Martínez-Horta, S., Pérez-González, R., Horta-Barba, A., Campolongo, A., Izquierdo, C., Pagonabarraga, J., Gómez-Ansón, B., & Kulisevsky, J. (2021). Cortical microstructural correlates of plasma neurofilament light chain in Huntington's disease. *Parkinsonism & Related Disorders*, *85*, 91–94. https://doi.org/10.1016/j.parkreldis.2021.03.008

Santangelo, G., D'Iorio, A., Maggi, G., Cuoco, S., Pellecchia, M. T., Amboni, M., Barone, P., & Vitale, C. (2018). Cognitive correlates of "pure apathy" in Parkinson's disease. *Parkinsonism & Related Disorders*, *53*, 101–104. https://doi.org/10.1016/j.parkreldis.2018.04.023

Santangelo, G., D'Iorio, A., Piscopo, F., Cuoco, S., Longo, K., Amboni, M., Baiano, C., Tafuri, D., Pellecchia, M. T., Barone, P., & Vitale, C. (2017). Assessment of apathy minimising the effect of motor dysfunctions in Parkinson's disease: A validation study of the dimensional apathy scale. *Quality of Life Research*, *26*(9), 2533–2540. https://doi.org/10.1007/s11136-017-1569-6

Santangelo, G., Siciliano, M., Trojano, L., Femiano, C., Monsurrò, M. R., Tedeschi, G., & Trojsi, F. (2017). Apathy in amyotrophic lateral sclerosis: Insights from Dimensional Apathy Scale. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *18*(5–6), 434–442. https://doi.org/10.1080/21678421.2017.1313865

Santangelo, G., Vitale, C., Trojano, L., Errico, D., Amboni, M., Barbarulo, A. M., Grossi, D., & Barone, P. (2012). Neuropsychological correlates of theory of mind in patients with early Parkinson's disease. *Movement Disorders*, *27*(1), 98–105. https://doi.org/10.1002/mds.23949

Scahill, R. I., Hobbs, N. Z., Say, M. J., Bechtel, N., Henley, S. M. D., Hyare, H., Langbehn, D. R., Jones, R., Leavitt, B. R., Roos, R. A. C., Durr, A., Johnson, H., Lehéricy, S., Craufurd, D., Kennard, C., Hicks, S. L., Stout, J. C., Reilmann, R., & Tabrizi, S. J. (2013). Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. *Human Brain Mapping*, *34*(3), 519–529. https://doi.org/10.1002/hbm.21449

Schmidt, L., d'Arc, B. F., Lafargue, G., Galanaud, D., Czernecki, V., Grabli, D., Schüpbach, M., Hartmann, A., Lévy, R., Dubois, B., & Pessiglione, M. (2008). Disconnecting force from money: Effects of basal ganglia damage on incentive motivation. *Brain*, *131*(5), 1303–1310. https://doi.org/10.1093/brain/awn045

Schmidt, L., Lebreton, M., Cléry-Melin, M.-L., Daunizeau, J., & Pessiglione, M. (2012). Neural mechanisms underlying motivation of mental versus physical effort. *PLoS Biology*, *10*(2). https://doi.org/10.1371/journal.pbio.1001266

Schobel, S. A., Palermo, G., Auinger, P., Long, J. D., Ma, S., Khwaja, O. S., Trundell, D., Cudkowicz, M., Hersch, S., Sampaio, C., Dorsey, E. R., Leavitt, B. R., Kieburtz, K. D., Sevigny, J. J., Langbehn, D. R., Tabrizi, S. J., & For the TRACK-HD, COHORT, CARE-HD, and 2CARE Huntington Study Group Investigators. (2017). Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology*, *89*(24), 2495–2502. https://doi.org/10.1212/WNL.0000000000004743

Segalàs, C., Cernadas, E., Puialto, M., Fernández-Delgado, M., Arrojo, M., Bertolin, S., Real, E., Menchón, J. M., Carracedo, A., Tubío-Fungueiriño, M., Alonso, P., & Fernández-Prieto, M. (2024). Cognitive and clinical predictors of a long-term course in obsessive compulsive disorder: A machine learning approach in a prospective cohort study. *Journal of Affective Disorders*, *350*, 648–655. https://doi.org/10.1016/j.jad.2024.01.157

Sellers, J., Ridner, S. H., & Claassen, D. O. (2020). A systematic review of neuropsychiatric symptoms and functional capacity in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *32*(2), 109–124. https://doi.org/10.1176/appi.neuropsych.18120319

Sen, P. N., & Basser, P. J. (2005). A model for diffusion in white matter in the brain. *Biophysical Journal*, *89*(5), 2927–2938. https://doi.org/10.1529/biophysj.105.063016

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., Mintun, M. A., Wang, S., Coalson, R. S., & Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, *106*(6), 1942–1947. https://doi.org/10.1073/pnas.0812686106

Shin, J. H., Shin, S. A., Lee, J.-Y., Nam, H., Lim, J.-S., & Kim, Y. K. (2017). Precuneus degeneration and isolated apathy in patients with Parkinson's disease. *Neuroscience Letters*, *653*, 250–257. https://doi.org/10.1016/j.neulet.2017.05.061

Siebzehnrübl, F. A., Raber, K. A., Urbach, Y. K., Schulze-Krebs, A., Canneva, F., Moceri, S., Habermeyer, J., Achoui, D., Gupta, B., Steindler, D. A., Stephan, M., Nguyen, H. P., Bonin, M., Riess, O., Bauer, A., Aigner, L., Couillard-Despres, S., Paucar, M. A., Svenningsson, P., … Hörsten, S. von. (2018). Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition. *Proceedings of the National Academy of Sciences*, *115*(37), E8765–E8774. https://doi.org/10.1073/pnas.1807962115

Siegel, J. S., Snyder, A. Z., Metcalf, N. V., Fucetola, R. P., Hacker, C. D., Shimony, J. S., Shulman, G. L., & Corbetta, M. (2014). The circuitry of abulia: Insights from functional connectivity MRI. *NeuroImage: Clinical*, *6*, 320–326. https://doi.org/10.1016/j.nicl.2014.09.012

Sierpowska, J., Gabarrós, A., Fernandez-Coello, A., Camins, À., Castañer, S., Juncadella, M., de Diego-Balaguer, R., & Rodríguez-Fornells, A. (2015). Morphological derivation overflow as a result of disruption of the left frontal aslant white matter tract. *Brain and Language*, *142*, 54–64. https://doi.org/10.1016/j.bandl.2015.01.005

Simon, J. J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., & Kaiser, S. (2010). Neural correlates of reward processing in schizophrenia—Relationship to apathy and depression. *Schizophrenia Research*, *118*(1), 154–161. https://doi.org/10.1016/j.schres.2009.11.007

Simpson, J., Dale, M., Theed, R., Gunn, S., Zarotti, N., & Eccles, F. J. R. (2019). Validity of irritability in Huntington's disease: A scoping review. *Cortex*, *120*, 353–374. https://doi.org/10.1016/j.cortex.2019.06.012

Singh-Bains, M. K., Tippett, L. J., Hogg, V. M., Synek, B. J., Roxburgh, R. H., Waldvogel, H. J., & Faull, R. L. M. (2016). Globus pallidus degeneration and clinicopathological features of Huntington disease. *Annals of Neurology*, *80*(2), 185–201. https://doi.org/10.1002/ana.24694

Sinha, N., Manohar, S., & Husain, M. (2013). Impulsivity and apathy in Parkinson's disease. *Journal of Neuropsychology*, *7*(2), 255–283. https://doi.org/10.1111/jnp.12013

Sitek, E. J., Thompson, J. C., Craufurd, D., & Snowden, J. S. (2014). Unawareness of deficits in Huntington's disease. *Journal of Huntington's Disease*, *3*(2), 125–135. https://doi.org/10.3233/JHD-140109

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *77*(5), 579–584. https://doi.org/10.1136/jnnp.2005.075929

Soliveri, P., Paridi, D., Del Sorbo, F., Tramacere, I., & Girotti, F. (2022). Negative symptoms in Huntington's disease. *Neurological Sciences*, *43*(6), 3695–3701. https://doi.org/10.1007/s10072-021-05787-x

Sousa, M., Moreira, F., Jesus-Ribeiro, J., Marques, I., Cunha, F., Canário, N., Freire, A., & Januário, C. (2017). Apathy profile in Parkinson's and Huntington's disease: A comparative cross-sectional study. *European Neurology*, *79*(1–2), 13–20. https://doi.org/10.1159/000481981

Spiegel, D. R., Warren, A., & Servidio, L. (2018). Disorders of diminished motivation: What they are, and how to treat them. *Current Psychiatry*, *17*(1), 10–18.

Stanton, B. R., & Carson, A. (2016). Apathy: A practical guide for neurologists. *Practical Neurology*, *16*(1), 42–47. https://doi.org/10.1136/practneurol-2015-001232

Stanton, B. R., Leigh, P. N., Howard, R. J., Barker, G. J., & Brown, R. G. (2013). Behavioural and emotional symptoms of apathy are associated with distinct patterns of brain atrophy in neurodegenerative disorders. *Journal of Neurology*, *260*(10), 2481–2490. https://doi.org/10.1007/s00415-013-6989-9

Starkstein, S. E. (2000). Apathy and withdrawal. *International Psychogeriatrics*, *12*(S1), 135–137. https://doi.org/10.1017/S1041610200006918

Starkstein, S. E., Brockman, S., Bruce, D., & Petracca, G. (2010). Anosognosia Is a significant predictor of apathy in Alzheimer's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(4), 378–383. https://doi.org/10.1176/jnp.2010.22.4.378

Starkstein, S. E., Ingram, L., Garau, M. L., & Mizrahi, R. (2005). On the overlap between apathy and depression in dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(8), 1070–1074. https://doi.org/10.1136/jnnp.2004.052795

Starkstein, S. E., Jorge, R., & Mizrahi, R. (2006). The prevalence, clinical correlates and treatment of apathy in Alzheimer's disease. *The European Journal of Psychiatry*, *20*(2), 96–106.

Starkstein, S. E., & Leentjens, A. F. G. (2008). The nosological position of apathy in clinical practice. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(10), 1088–1092. https://doi.org/10.1136/jnnp.2007.136895

Starkstein, S. E., Mayberg, H. S., Preziosi, T. J., Andrezejewski, P., Leiguarda, R., & Robinson, R. G. (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *Journal of Neuropsychiatry*, *4*(2).

Steffens, D. C., Fahed, M., Manning, K. J., & Wang, L. (2022). The neurobiology of apathy in depression and neurocognitive impairment in older adults: A review of epidemiological, clinical, neuropsychological and biological research. *Translational Psychiatry*, *12*(1), 1–16. https://doi.org/10.1038/s41398-022-02292-3

Stella, F., Radanovic, M., Aprahamian, I., Canineu, P. R., de Andrade, L. P., & Forlenza, O. V. (2014). Neurobiological correlates of apathy in Alzheimer's disease and Mild Cognitive Impairment: A critical review. *Journal of Alzheimer's Disease*, *39*(3), 633–648. https://doi.org/10.3233/JAD-131385

Stern, C. E., & Passingham, R. E. (1996). The nucleus accumbens in monkeys (*Macaca fascicularis*): II. Emotion and motivation. *Behavioural Brain Research*, *75*(1), 179–193. https://doi.org/10.1016/0166-4328(96)00169-6

Stevens, F. L. (2011). Anterior cingulate cortex: Unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci*, 6.

Steventon, J. J., Trueman, R. C., Rosser, A. E., & Jones, D. K. (2016). Robust MR-based approaches to quantifying white matter structure and structure/function alterations in Huntington's disease. *Journal of Neuroscience Methods*, *265*, 2–12. https://doi.org/10.1016/j.jneumeth.2015.08.027

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., Aylward, E. H., & The PREDICT-HD Investigators and Coordinators of the Huntington Study Group. (2011). Neurocognitive signs in prodromal Huntington disease. *Neuropsychology*, *25*(1), 1–14. https://doi.org/10.1037/a0020937

Strauss, G. P., Waltz, J. A., & Gold, J. M. (2014). A review of reward processing and motivational impairment in schizophrenia. *Schizophrenia Bulletin*, *40*(Suppl 2), S107–S116. https://doi.org/10.1093/schbul/sbt197

Strauss, M. E., & Sperry, S. D. (2002). An informant-based assessment of apathy in Alzheimer disease. *Cognitive and Behavioral Neurology*, *15*(3), 176.

Stuss, D. T. (2011). Functions of the frontal lobes: Relation to executive functions. *Journal of the International Neuropsychological Society*, *17*(05), 759–765. https://doi.org/10.1017/S1355617711000695

Stuss, D. T., & Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society B: Biological Sciences*, *362*(1481), 901–915. https://doi.org/10.1098/rstb.2007.2096

Stuss, D. T., Floden, D., Alexander, M. P., Levine, B., & Katz, D. (2001). Stroop performance in focal lesion patients: Dissociation of processes and frontal lobe lesion location. *Neuropsychologia*, *39*(8), 771–786. https://doi.org/10.1016/S0028-3932(01)00013-6

Stuss, D. T., Van Reekum, R., & Murphy, K. (2000). *The neuropsychology of emotion* (J. Borod, Ed.; pp. 340–363). Oxford University Press.

Sun, H.-H., Pan, P.-L., Hu, J.-B., Chen, J., Wang, X.-Y., & Liu, C.-F. (2020). Alterations of regional homogeneity in Parkinson's disease with "pure" apathy: A resting-state fMRI study. *Journal of Affective Disorders*, *274*, 792–798. https://doi.org/10.1016/j.jad.2020.05.145

Szymkowicz, S. M., Dotson, V. M., Jones, J. D., Okun, M. S., & Bowers, D. (2018). Symptom dimensions of depression and apathy and their relationship with cognition in Parkinson's disease. *Journal of the International Neuropsychological Society*, *24*(03), 269–282. https://doi.org/10.1017/S1355617717001011

Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., & Stout, J. C. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet Neurology*, *8*(9), 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X

Tabrizi, S. J., Reilmann, R., Roos, R. A., Durr, A., Leavitt, B., Owen, G., Jones, R., Johnson, H., Craufurd, D., Hicks, S. L., Kennard, C., Landwehrmeyer, B., Stout, J. C., Borowsky, B., Scahill, R. I., Frost, C., & Langbehn, D. R. (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24 month observational data. *The Lancet Neurology*, *11*(1), 42–53. https://doi.org/10.1016/S1474-4422(11)70263-0

Tabrizi, S. J., Scahill, R. I., Durr, A., Roos, R. A., Leavitt, B. R., Jones, R., Landwehrmeyer, G. B., Fox, N. C., Johnson, H., Hicks, S. L., Kennard, C., Craufurd, D., Frost, C., Langbehn, D. R., Reilmann, R., & Stout, J. C. (2011). Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: The 12-month longitudinal analysis. *The Lancet Neurology*, *10*(1), 31–42. https://doi.org/10.1016/S1474-4422(10)70276-3

Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J. C., & Langbehn, D. R. (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. *The Lancet Neurology*, *12*(7), 637–649. https://doi.org/10.1016/S1474-4422(13)70088-7

Tabrizi, S. J., Schobel, S., Gantman, E. C., Mansbach, A., Borowsky, B., Konstantinova, P., Mestre, T. A., Panagoulias, J., Ross, C. A., Zauderer, M., Mullin, A. P., Romero, K., Sivakumaran, S., Turner, E. C., Long, J. D., & Sampaio, C. (2022). A biological classification of Huntington's disease: The Integrated Staging System. *The Lancet Neurology*, *21*(7), 632–644. https://doi.org/10.1016/S1474-4422(22)00120-X

Tekin, S., & Cummings, J. L. (2002). Frontal–subcortical neuronal circuits and clinical neuropsychiatry: An update. *Journal of Psychosomatic Research*, *53*(2), 647–654.

Tetreault, A. M., Phan, T., Orlando, D., Lyu, I., Kang, H., Landman, B., Darby, R. R., & on behalf of Alzheimer's Disease Neuroimaging Initiative. (2020). Network localization of clinical, cognitive, and neuropsychiatric symptoms in Alzheimer's disease. *Brain*, *143*(4), 1249–1260. https://doi.org/10.1093/brain/awaa058

Thaler, D. E., Rolls, E. T., & Passingham, R. E. (1988). Neuronal activity of the supplementary motor area (SMA) during internally and externally triggered wrist movements. *Neuroscience Letters*, *93*(2), 264–269. https://doi.org/10.1016/0304-3940(88)90093-6

Thant, T., & Yager, J. (2019). Updating apathy: Using Research Domain Criteria to inform clinical assessment and diagnosis of disorders of motivation. *Journal of Nervous & Mental Disease*, *207*(9), 707–714. https://doi.org/10.1097/NMD.0000000000000860

The Huntington Study Group PHAROS Investigators, Biglan, K. M., Shoulson, I., Kieburtz, K., Oakes, D., Kayson, E., Shinaman, M. A., Zhao, H., Romer, M., Young, A., Hersch, S., Penney, J., Marder, K., Paulsen, J., Quaid, K., Siemers, E., Tanner, C., Mallonee, W., Suter, G., … Shults, C. (2016). Clinical-genetic associations in the Prospective Huntington at Risk Observational Study (PHAROS): Implications for clinical trials. *JAMA Neurology*, *73*(1), 102. https://doi.org/10.1001/jamaneurol.2015.2736

Theleritis, C., Politis, A., Siarkos, K., & Lyketsos, C. G. (2014). A review of neuroimaging findings of apathy in Alzheimer's disease. *International Psychogeriatrics*, *26*(2), 195–207. https://doi.org/10.1017/S1041610213001725

Thompson, J. C., Harris, J., Sollom, A. C., Stopford, C. L., Howard, E., Snowden, J. S., & Craufurd, D. (2012). Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J Neuropsychiatry Clin Neurosci*, 8.

Thompson, J. C., Snowden, J. S., Craufurd, D., & Neary, D. (2002). Behavior in Huntington's disease: Dissociating cognition-based and mood-based changes. *J Neuropsychiatry Clin Neurosci*, 7.

Thu, D. C. V., Oorschot, D. E., Tippett, L. J., Nana, A. L., Hogg, V. M., Synek, B. J., Luthi-Carter, R., Waldvogel, H. J., & Faull, R. L. M. (2010). Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington's disease. *Brain: A Journal of Neurology*, *133*(Pt 4), 1094–1110. https://doi.org/10.1093/brain/awq047

Tippett, L. J., Waldvogel, H. J., Thomas, S. J., Hogg, V. M., van Roon-Mom, W., Synek, B. J., Graybiel, A. M., & Faull, R. L. M. (2007). Striosomes and mood dysfunction in Huntington's disease. *Brain: A Journal of Neurology*, *130*(Pt 1), 206–221. https://doi.org/10.1093/brain/awl243

Toh, E. A., MacAskill, M. R., Dalrymple-Alford, J. C., Myall, D. J., Livingston, L., Macleod, S. A., & Anderson, T. J. (2014). Comparison of cognitive and UHDRS measures in monitoring

disease progression in Huntington's disease: A 12-month longitudinal study. *Translational Neurodegeneration*, *3*, 15. https://doi.org/10.1186/2047-9158-3-15

Treadway, M. T., & Zald, D. H. (2011). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience & Biobehavioral Reviews*, *35*(3), 537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006

Tumati, S., Martens, S., De Jong, B. M., & Aleman, A. (2019). Lateral parietal cortex in the generation of behavior: Implications for apathy. *Progress in Neurobiology*, *175*, 20–34. https://doi.org/10.1016/j.pneurobio.2018.12.003

Tung, J. Y., Rose, R. V., Gammada, E., Lam, I., Roy, E. A., Black, S. E., & Poupart, P. (2014). Measuring life space in older adults with mild-to-moderate Alzheimer's disease using mobile phone GPS. *Gerontology*, *60*(2), 154–162. https://doi.org/10.1159/000355669

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, *15*(1), 273–289.

Unschuld, P. G., Joel, S. E., Pekar, J. J., Reading, S. A., Oishi, K., McEntee, J., Shanahan, M., Bakker, A., Margolis, R. L., Bassett, S. S., Rosenblatt, A., Mori, S., van Zijl, P. C., Ross, C. A., & Redgrave, G. W. (2012). Depressive symptoms in prodromal Huntington's Disease correlate with Stroop-interference related functional connectivity in the ventromedial prefrontal cortex. *Psychiatry Research: Neuroimaging*, *203*(2), 166–174. https://doi.org/10.1016/j.pscychresns.2012.01.002

Ursu, S., & Carter, C. S. (2005). Outcome representations, counterfactual comparisons and the human orbitofrontal cortex: Implications for neuroimaging studies of decision-making. *Cognitive Brain Research*, *23*(1), 51–60. https://doi.org/10.1016/j.cogbrainres.2005.01.004

van der Linde, R. M., Matthews, F. E., Dening, T., & Brayne, C. (2017). Patterns and persistence of behavioural and psychological symptoms in those with cognitive impairment: The

importance of apathy. *International Journal of Geriatric Psychiatry*, *32*(3), 306–315. https://doi.org/10.1002/gps.4464

van der Mast, R. C., Vinkers, D. J., Stek, M. L., Bek, M. C., Westendorp, R. G. J., Gussekloo, J., & de Craen, A. J. M. (2008). Vascular disease and apathy in old age. The Leiden 85-plus Study. *International Journal of Geriatric Psychiatry*, *23*(3), 266–271. https://doi.org/10.1002/gps.1872

van Duijn, E. (2010). Treatment of irritability in Huntington's disease. *Current Treatment Options in Neurology*, *12*(5), 424–433. https://doi.org/10.1007/s11940-010-0088-3

van Duijn, E., Craufurd, D., Hubers, A. A. M., Giltay, E. J., Bonelli, R., Rickards, H., Anderson, K. E., van Walsem, M. R., van der Mast, R. C., Orth, M., Landwehrmeyer, G. B., & European Huntington's Disease Network Behavioural Phenotype Working Group. (2014). Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(12), 1411–1418. https://doi.org/10.1136/jnnp-2013-307343

van Duijn, E., Reedeker, N., Giltay, E. J., Eindhoven, D., Roos, R. A. C., & van der Mast, R. C. (2013). Course of irritability, depression and apathy in Huntington's disease in relation to motor symptoms during a two-year follow-up period. *Neurodegenerative Diseases*. https://doi.org/10.1159/000343210

van Duijn, E., Reedeker, N., Giltay, E. J., Roos, R. a. C., & van der Mast, R. C. (2010). Correlates of apathy in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(3), 287–294. https://doi.org/10.1176/jnp.2010.22.3.287

van Duijn, E., Vrijmoeth, E. M., Giltay, E. J., & Bernhard Landwehrmeyer, G. (2018). Suicidal ideation and suicidal behavior according to the C-SSRS in a European cohort of Huntington's disease gene expansion carriers. *Journal of Affective Disorders*, *228*, 194–204. https://doi.org/10.1016/j.jad.2017.11.074

van Reekum, R., Stuss, D. T., & Ostrander, L. (2005). Apathy: Why care? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(1), 7–19. https://doi.org/10.1176/jnp.17.1.7

Varanese, S., Perfetti, B., Ghilardi, M. F., & Di Rocco, A. (2011). Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. *PLoS ONE*, *6*(3), e17846. https://doi.org/10.1371/journal.pone.0017846

Vassena, E., Silvetti, M., Boehler, C. N., Achten, E., Fias, W., & Verguts, T. (2014). Overlapping neural systems represent cognitive effort and reward anticipation. *PLoS ONE*, *9*(3), e91008. https://doi.org/10.1371/journal.pone.0091008

Vinther-Jensen, T., Larsen, I. U., Hjermind, L. E., Budtz-Jørgensen, E., Nielsen, T. T., Nørremølle, A., Nielsen, J. E., & Vogel, A. (2014). A clinical classification acknowledging neuropsychiatric and cognitive impairment in Huntington's disease. *Orphanet Journal of Rare Diseases*, *9*(1). https://doi.org/10.1186/s13023-014-0114-8

Vogt, B. A. (2016). Midcingulate cortex: Structure, connections, homologies, functions and diseases. *Journal of Chemical Neuroanatomy*, *74*, 28–46. https://doi.org/10.1016/j.jchemneu.2016.01.010

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain*, *136*(6), 1692–1707. https://doi.org/10.1093/brain/awt094

von Giesen, H.-J., Schlaug, G., Steinmetz, H., Benecke, R., Freund, H.-J., & Seitz, R. J. (1994). Cerebral network underlying unilateral motor neglect: Evidence from positron emission tomography. *Journal of the Neurological Sciences*, *125*(1), 29–38. https://doi.org/10.1016/0022-510X(94)90238-0

Vonsattel, J. P. G., & DiFiglia, M. (1998). Huntington disease. *Journal of Neuropathology and Experimental Neurology*, *57*(5), 369–384.

Vonsattel, J. P. G., Myers, R. H., Stevens, T. J., Ferrante, R. J., Bird, E. D., & Richardson, E. P., Jr. (1985). Neuropathological classification of Huntington's disease. *Journal of Neuropathology &*

Experimental Neurology, *44*(6), 559–577. https://doi.org/10.1097/00005072-198511000-00003

Wager, T. D., Phan, K. L., Liberzon, I., & Taylor, S. F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: A meta-analysis of findings from neuroimaging. *NeuroImage*, *19*(3), 513–531. https://doi.org/10.1016/S1053-8119(03)00078-8

Waldvogel, H. J., Kim, E. H., Thu, D. C. V., Tippett, L. J., & Faull, R. L. M. (2012). New perspectives on the neuropathology in Huntington's disease in the human brain and its relation to symptom variation. *Journal of Huntington's Disease*, *1*(2), 143–153. https://doi.org/10.3233/JHD-2012-120018

Waldvogel, H. J., Kim, E. H., Tippett, L. J., Vonsattel, J.-P. G., & Faull, R. L. (2014). The neuropathology of Huntington's disease. In H. H. P. Nguyen & M. A. Cenci (Eds.), *Behavioral Neurobiology of Huntington's Disease and Parkinson's Disease* (Vol. 22, pp. 33–80). Springer Berlin Heidelberg. https://doi.org/10.1007/7854_2014_354

Wei, G., Irish, M., Hodges, J. R., Piguet, O., & Kumfor, F. (2019). Disease-specific profiles of apathy in Alzheimer's disease and behavioural-variant frontotemporal dementia differ across the disease course. *Journal of Neurology*. https://doi.org/10.1007/s00415-019-09679-1

Weintraut, R., Karádi, K., Lucza, T., Kovács, M., Makkos, A., Janszky, J., & Kovács, N. (2016). Lille Apathy Rating Scale and MDS-UPDRS for screening apathy in Parkinson's disease. *Journal of Parkinson's Disease*, *6*(1), 257–265. https://doi.org/10.3233/JPD-150726

Weller, J. A., Levin, I. P., Shiv, B., & Bechara, A. (2009). The effects of insula damage on decision-making for risky gains and losses. *Social Neuroscience*, *4*(4), 347–358. https://doi.org/10.1080/17470910902934400

Wong, S., Wei, G., Husain, M., Hodges, J. R., Piguet, O., Irish, M., & Kumfor, F. (2023). Altered reward processing underpins emotional apathy in dementia. *Cognitive, Affective, & Behavioral Neuroscience*, *23*(2), 354–370. https://doi.org/10.3758/s13415-022-01048-2

Wongpakaran, N., van Reekum, R., Wongpakaran, T., & Clarke, D. (2007). Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: A case-control study. *Annals of General Psychiatry*, *6*(1), 7. https://doi.org/10.1186/1744-859X-6-7

Wood, S., Cummings, J. L., Hsu, M.-A., Barclay, T., Wheatley, M. V., Yarema, K. T., & Schnelle, J. F. (2000). The use of the Neuropsychiatric Inventory in nursing home residents: Characterization and measurement. *The American Journal of Geriatric Psychiatry*, *8*(1), 75–83. https://doi.org/10.1097/00019442-200002000-00010

World Health Organization. (1993). *The ICD-10 classification of mental and behavioural disorders*. World Health Organization.

Yamamoto, A., Lucas, J. J., & Hen, R. (2000). Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell*, *101*(1), 57–66. https://doi.org/10.1016/S0092-8674(00)80623-6

Yan, H., Wu, H., Cai, Z., Du, S., Li, L., Xu, B., Chang, C., & Wang, N. (2023). The neural correlates of apathy in the context of aging and brain disorders: A meta-analysis of neuroimaging studies. *Frontiers in Aging Neuroscience*, *15*, 1181558. https://doi.org/10.3389/fnagi.2023.1181558

Yang, S., Hua, P., Shang, X., Cui, Z., Zhong, S., Gong, G., & William Humphreys, G. (2015). Deficiency of brain structural sub-network underlying post-ischaemic stroke apathy. *European Journal of Neurology*, *22*(2), 341–347. https://doi.org/10.1111/ene.12575

Yazbek, H., Norton, J., Capdevielle, D., Larue, A., Boulenger, J.-P., Gély-Nargeot, M.-C., & Raffard, S. (2014). The Lille Apathy Rating Scale (LARS): Exploring its psychometric properties in schizophrenia. *Schizophrenia Research*, *157*(1), 278–284. https://doi.org/10.1016/j.schres.2014.04.034

Yi, H.-G., Maddox, W. T., Mumford, J. A., & Chandrasekaran, B. (2016). The role of corticostriatal systems in speech category learning. *Cerebral Cortex (New York, NY)*, *26*(4), 1409–1420. https://doi.org/10.1093/cercor/bhu236

Young, A. B., Penney, J. B., Starosta-Rubinstein, S., Markel, D. S., Berent, S., Giordani, B., Ehrenkaufer, R., Jewett, D., & Hichwa, R. (1986). PET scan investigations of Huntington's disease: Cerebral metabolic correlates of neurological features and functional decline. *Annals of Neurology*, *20*(3), 296–303. https://doi.org/10.1002/ana.410200305

Youssov, K., Audureau, E., Vandendriessche, H., Morgado, G., Layese, R., Goizet, C., Verny, C., Bourhis, M.-L., & Bachoud-Lévi, A.-C. (2022). The burden of Huntington's disease: A prospective longitudinal study of patient/caregiver pairs. *Parkinsonism & Related Disorders*, *103*, 77–84. https://doi.org/10.1016/j.parkreldis.2022.08.023

Yuen, G. S., Gunning, F. M., Woods, E., Klimstra, S. A., Hoptman, M. J., & Alexopoulos, G. S. (2014). Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *Journal of Affective Disorders*, *166*, 179–186. https://doi.org/10.1016/j.jad.2014.05.008

Zahodne, L. B., Bernal-Pacheco, O., Bowers, D., Ward, H., Oyama, G., Limotai, N., Velez-Lago, F., Rodriguez, R. L., Malaty, I., McFarland, N. R., & Okun, M. S. (2012). Are selective serotonin reuptake inhibitors associated with greater apathy in Parkinson's disease? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *24*(3), 326–330. https://doi.org/10.1176/appi.neuropsych.11090210

Zamboni, G., Huey, E. D., Krueger, F., Nichelli, P. F., & Grafman, J. (2008). Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. *Neurology*, *71*(10), 736–742. https://doi.org/10.1212/01.wnl.0000324920.96835.95

Zappacosta, B., Monza, D., Meoni, C., Austoni, L., Soliveri, P., Gellera, C., Alberti, R., Mantero, M., Penati, G., Caraceni, T., & Girotti, F. (1996). Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease. *Archives of Neurology*, *53*(6), 493–497. https://doi.org/10.1001/archneur.1996.00550060035012

Zeghari, R., Manera, V., Fabre, R., Guerchouche, R., König, A., Phan Tran, M. K., & Robert, P. (2020). The "Interest Game": A ludic application to improve apathy assessment in patients with

neurocognitive disorders. *Journal of Alzheimer's Disease*, *74*(2), 669–677. https://doi.org/10.3233/JAD-191282

Zeitzer, J. M., David, R., Friedman, L., Mulin, E., Garcia, R., Wang, J., Yesavage, J. A., Robert, P. H., & Shannon, W. (2013). Phenotyping apathy in individuals with Alzheimer disease using functional principal component analysis. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *21*(4), 391–397. https://doi.org/10.1016/j.jagp.2012.12.012

Zeun, P., McColgan, P., Dhollander, T., Gregory, S., Johnson, E. B., Papoutsi, M., Nair, A., Scahill, R. I., Rees, G., & Tabrizi, S. J. (2022). Timing of selective basal ganglia white matter loss in premanifest Huntington's disease. *NeuroImage : Clinical*, *33*, 102927. https://doi.org/10.1016/j.nicl.2021.102927

Zeun, P., Scahill, R. I., Tabrizi, S. J., & Wild, E. J. (2019). Fluid and imaging biomarkers for Huntington's disease. *Molecular and Cellular Neuroscience*, *97*, 67–80. https://doi.org/10.1016/j.mcn.2019.02.004

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., Mattis, P. J., Gordon, M. F., Feigin, A., & Eidelberg, D. (2006). An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*. https://doi.org/10.1080/13803390500246910

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., Rocco, M., Mattis, P. J., Gordon, M. F., Feigin, A. S., & Eidelberg, D. (2007). Relationship between self-reported apathy and executive dysfunction in nondemented patients with Parkinson disease. *Cognitive and Behavioral Neurology : Official Journal of the Society for Behavioral and Cognitive Neurology*, *20*(3), 184–192. https://doi.org/10.1097/WNN.0b013e318145a6f6

Zhang, J., Gregory, S., Scahill, R. I., Durr, A., Thomas, D. L., Lehericy, S., Rees, G., Tabrizi, S. J., Zhang, H., & the TrackOn-HD investigators. (2018). In vivo characterization of white matter pathology in premanifest Huntington's disease. *Annals of Neurology*. https://doi.org/10.1002/ana.25309

Zhang, Y., Long, J. D., Mills, J. A., Warner, J. H., Lu, W., & Paulsen, J. S. (2011). Indexing disease progression at study entry with individuals at-risk for Huntington disease. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, *156*(7), 751–763. https://doi.org/10.1002/ajmg.b.31232

Zielonka, D., Mielcarek, M., & Landwehrmeyer, G. B. (2015). Update on Huntington's disease: Advances in care and emerging therapeutic options. *Parkinsonism & Related Disorders*, *21*(3), 169–178. https://doi.org/10.1016/j.parkreldis.2014.12.013

List of Tables

Table 1.1. Dimensional definitions of apathy 25
Table 1.2. Proposed diagnostic criteria for apathy through the ages 31
Table 1.3. Apathy scales and dimensions assessed 35
Table 1.4. Summary of neural correlates of apathy in Huntington's disease 56
Table 2.1. Overview of how three Research Aims were addressed by each Study 68
Table 4.1. Sociodemographic and clinical characteristics of study participants 89
Table 4.2. Behavioral results for three participant groups 97
Table 4.3. Lack of age effect on apathy levels 97
Table 4.4. Mean FA and MD diffusion values in manifest Huntington's disease patients and controls 98
Table 5.1. Sociodemographic information at baseline 112
Table 5.2. Sociodemographic information for longitudinal VBM cohort (at baseline) 118
Table 5.3. Longitudinal VBM of GMV and PBA-s apathy in premanifest HD individuals 121
Table 5.4. Cross-sectional VBM analysis of GMV and PBA-s apathy 122
Table 5.5. Apathy and cognitive decline as predicted by right MCC volume 122
Table 5.6. Apathy as predicted by cognitive decline 125
Table 6.1. Sociodemographic and clinical characteristics of study participants 138
Table 6.2. Principal component analysis of LARS-s items, rotated component matrix 143
Table 6.3. VBM analysis of GMV and global apathy severity 146
Table 6.4. VBM analysis of GMV and apathy severity across profiles 147
Table 7.1. Sociodemographic and clinical characteristics of study participants (initial value) 160
Table 7.2. Cluster metrics of shared psychiatric evolution 168

List of Figures

Figure 1.1. Chronological development of apathy instruments and diagnostic criteria from 1991 to present day 34
Figure 1.2. Three-dimensional model of apathy & proposed neurobiological correlates .. 42
Figure 1.3. Structures of the striatum and associated frontostriatal circuits 50
Figure 1.4. Whole brain and regional atrophy in HD groups compared to a healthy control 51
Figure 1.5. Structural neural correlates associated with apathy in Huntington's disease . 59
Figure 4.1. Three cortico-striatal tracts of interest 93
Figure 4.2. Levels of apathy across participant groups 96
Figure 4.3. Positive relationship between apathy levels and white matter disturbance in the three tracts of interest 100
Figure 5.1. Raw longitudinal data for each participant. 119
Figure 5.2. Specific gray matter atrophy in the right MCC relates with increasing apathy severity over time 120
Figure 5.3. Results of cross-sectional voxel-based morphometry analysis with structural T1-weighted images 121
Figure 5.4. Smaller initial MCC volume predicts a faster rate of apathy development across time 125
Figure 6.1. Principal component analysis of LARS-s produces clinically meaningful apathy profiles 143
Figure 6.2. Gray matter volume negatively associated with global apathy 145
Figure 6.3. Gray matter volume negatively related with apathy profiles. 146
Figure 7.1. Alignment of temporal sequences with dynamic time warping highlights psychiatric trajectories 163
Figure 7.2. Heatmaps depicting clustering performance at sequential combinations of λ and *threshold* values 165
Figure 7.3. Unsupervised clustering produced eleven clusters 167
Figure 7.4. Psychiatric signatures in the two main clusters differ in overall behavioral abnormalities 169
Figure 7.5. Psychiatric signatures defined by unique trajectories in specific domains 170
Figure 7.6. Apathy and dysexecutive behaviors are positively correlated 171
Figure 8.1. Apathy subdimensions may arise from disruptions along inter-connected processes of goal-directed behavior 196

Cognition and Brain Plasticity Unit

UNIVERSITAT DE BARCELONA

PhD Program in Biomedicine (Neurosciences)

2024