UNIVERSITAT DE BARCELONA

Involvement of Foxp2 in the alterations of the basal ganglia circuitry in Huntington's Disease

Ened Rodríguez Urgellés

UNIVERSITAT DE BARCELONA

Involvement of Foxp2 in the alterations of the basal ganglia circuitry in Huntington's Disease

Doctoral degree of Biomedicine in the Facultat de Medicina de la Universitat de Barcelona.

Dissertation submitted by:

Ened Rodríguez Urgellés

This work was performed at the Department of Biomedicine in the Faculty of Medicina and Health Sciences under the supervision of Dr. Jordi Alberch Vié and Dr. Albert Giralt Torroella.

Ened Rodríguez Urgellés

Jordi Alberch Vié

Albert Giralt Torroella

A mi madre,

"Sólo entonces, cuando la mente es libre, libre de verdad, es cuando puede aprender; una mente así es a la vez el maestro y el discípulo"

Jiddu Krishnamurti

ABSTRACT

Huntington's Disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by motor, psychiatric, and cognitive manifestations. The disease is caused by an unstable expansion of the CAG trinucleotide repeat in the huntingtin gene (*Htt*), which eventually leads the HD patients to death, in a period of a few decades. Regardless the ubiquitous expression of mutant huntingtin (mHtt) in somatic tissues, the pathologic features are seemingly restricted to the brain. During the disease, the caudate and putamen (striatum in mice) suffers a progressive neuronal loss and atrophy. Later, other brain regions as cortex and hippocampus also become affected as the neuronal loss and atrophy are widely spread throughout the brain. As striatum is the main hub of basal ganglia circuit, which orchestrates the voluntary motor sequences along with cognitive and emotional responses, it is believed that striatum pathophysiology underlies the behavioral symptoms of the disease. Importantly, before neurodegeneration mHtt acts from the roots of cellular processes inducing the synaptic and neuronal dysfunction of the striatal neurons until death. Hence, we believed in the importance of deciphering the initial and triggering key mechanisms of the disease in prodromal stages and designing useful therapeutic strategies able to delay the onset of the neuropathologic changes and clinical symptoms in HD. Here, we identify a candidate gene named *Foxp2*, which has been shown to be strongly associated with basal ganglia circuitry in conjunction with psychiatric and motor deficits. We identified an early striatal downregulation of Foxp2 protein which seems to be linked to behavioral and molecular changes in the juvenile R6/1 mouse model. Juvenile R6/1 mice behavioral phenotype was characterized by an increased hyperlocomotive and impulsive-like behavior, less aggressive-like behavior and disrupted locomotor circadian rhythms concomitant with structural and functional changes as decreased dendritic spine density and dysregulation of striatal protein expression. Interestingly, the rescue of striatal Foxp2 levels reverted impulsivity-phenotype, likely by rescuing striatal protein expression dysregulation and synaptic plasticity impairment. We also detected a downregulation of Foxp2 protein in the thalamus of pre- and symptomatic R6/1 mouse. We confirmed the well-established cortico-striatal disconection previously found in HD models, but we also demonstrated the functional disconnection between the thalamus and the striatum at symptomatic stages of R6/1 mice. Recovery of Foxp2 in the ventrolateral thalamus rescued sensory-motor behavioral disturbances in the symptomatic R6/1 mice, along with structural and functional changes, whereas knockdown of Foxp2 mimicked HD-associated phenotype. In summary, our study points out Foxp2 as a potential target to understand the neuropathogenesis and behavioral deficits in HD.

ABBREVIATIONS

A2A	Adenosine A2A-like receptor
AAV	Adeno-associated virus
ADHD	Attention-deficit/hyperactivity disorder
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP	Antero-posterior axes
ARTP	Accelerating Rotarod Training Procedure
BAC	Bacterial artificial chromosome
BDNF	Brain-derived neurotrophic factor
BOLD	Blood oxygen level-dependent
Ca^{2+}	Calcium
CAG	Cytosine, Adenine, Guanine
CAS	Childhood apraxia of speech
CBP	CREB-binding protein
cDNA	Complementary DNA
ChAT	Choline acetyltransferase
CM-Pf	Centromedian-parafascicular complex
CNTNAP2	Contactin Associated Protein 2
CREB	cAMP-response element-binding protein
D1R	Dopamine D1-like receptor
D2R	Dopamine D2-like receptor
DARPP-32	Dopamine and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein
DAT	Dopamine transporter
DISC1	Disrupted in Schizophrenia 1
DMSO	Dimethyl Sulfoxide

DNA	Deoxyribonuclei acid
EAAT2	Excitatory amino acid transporter 2
EPSc	Excitatory post synaptic current
Fox	Forkhead box
Foxp1	Forkhead box protein P1
Foxp2	Forkhead box protein P2
FS	Fast-spiking interneuron
FST	Forced-swimming test
GABA	γ-aminobutyric acid
GFP	Green fluorescent protein
GLT-1	Glutamate transporter-1
GPe	External globus pallidus
GPi	Internal globus pallidus
GWAS	Genome-wide association studies
HAT	Histone acetyltransferase
HD	Huntington's disease
HDAC	Histone deacetylase
Hdh	Huntington's disease homolog
HEAT	Huntingtin, elongation factor 3, regulatory subunit A of protein phosphatase 2A, and TOR1
Htt	Huntingtin
IPSc	Inhibitory post synaptic current
JHD	Juvenile Huntington's Disease
kDa	Kilodalton
KI	Knock-in

KO	Knock-out
L	Lateral axes
LFP	Local field potential
LFS	Low frequency stimulation
LTD	Long-term depression
LTP	Long-term potentiation
MET	MET Proto-Oncogene, Receptor Tyrosine Kinase
mGluR	Metabotropic glutamate receptor
mHtt	Mutant huntingtin
MPTP	1-methyl4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSN	Medium spiny neuron
NAcc	Nucleus Accumbens
NLS	Nuclear localization signal
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NWDT	Novel Whisker Texture Discrimination Task
$p75^{NTR}$	p75 neutrophin receptor
PAX6	Paired Box 6
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PFA	Paraformaldehide
pLTS	Parvalbumin-negative low-threshold spiking interneuron
Po	Posterior thalamic nucleus

PolyQ	Polyglutamine
PSD-95	Post Synaptic Density 95
PV	Parvalbumin interneuron
QOL	Quality of life
RELN	Reelin
REST/NRSF	Repressor element-1 transcription factor/neuron restrictive silencer factor
Rpm	Rotations per minute
RT	Room Temperature
SEM	Standard Error of the Mean
SNc	Substantia nigra pars compacta
SNPs	Single nucleotide polymorphisms
SNr	Substantia nigra pars reticulata
SPPT	Spontaneous Place Preference Test
STEP	Enriched protein tyrosine Phosphatase
STN	Subthalamic nucleus
TBS	Tris-buffered Saline
TBZ	Tetrabenazine
TCF/LEF	T-cell factor/lymphoid enhancer factor
TrkB	Trompomosin receptor kinase
VGluT2	Vesicular glutamate transporter 2
VLDLR	Very-low-density-lipoprotein receptor gene
VMAT2	Vesicular monoamine transporter type 2
VP	Ventral posterior nucleus
WT	Wild-type
YAC	Yeast artificial chromosome

TABLE OF CONTENTS

INTRODUCTION

1. Huntington's Disease

Huntington's Disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by motor, behavioral, and cognitive manifestations (Walker, 2007). The first and thorough description of the motor symptoms was provided by the physician George Huntington in 1872, who decided to name the disease "chorea" (from the ancient Greek word choreia which means dance) based on the dancing propensities of the affected ones (Huntington, 1872). Through the past decades, non-motor symptoms such as psychiatric disturbances and cognitive impairment have been recognized and gained attention, resulting in a renaming of the disorder to HD (Novak & Tabrizi, 2011). Nowadays, HD treatment is still solely based on palliative symptomatic approaches to ameliorate motor and psychiatric disease symptoms.

1.1. Clinical Aspects

A systematic review and meta-analysis of HD cases around the word reveals an incidence of 0.38 per 100,000 per year, and a prevalence of 2.71 per 100,000 (Pringsheim et al., 2012), whereas Europe, North America, and Australia show the highest prevalence 5-10 per 100,00. A more recent report estimates that European prevalence is 10 per 100,000, and corroborate that global prevalence is 2.7 per 100,000 without considering data from African population. For example, Egypt has the highest global point prevalence at 21 per 100,000, at a rate twice as high as Europe and 11 times higher than the United States (Brady, 2019).

HD symptoms comprise psychiatric disturbances, motor dysfunction, and cognitive decline. The onset of symptoms is typically in middle age, between 30 and 50 years of age. A 10% of the patients develops symptoms before age 20, with increased severity as well as a faster disease progression. It is commonly known as a juvenile HD variant (JHD) (Conneally, 1984; Walker, 2007). Clinical manifestations as bradykinesia, dystonia or parkinsonian features may occur more frequently in juvenile HD, while chorea is commonly less present or absent. The juvenile HD patients particularly show unusual clinical manifestations compared with adult-onset HD patients as seizures, school failure and occasionally autism traits (Marano et al., 2017; Quarrell et al., 2013).

In the early stages, adult-onset HD patients develop personality changes encompassing a wide range of psychiatric and emotional disturbances inside the spectrum, which can precede the classical motor symptoms by up to a decade (Epping et al., 2016). HD individuals commonly report progressive weight loss, apathy, depression, anxiety, irritability, aggression,

psychosis, mania, suicidal ideation, disinhibition, impulsivity, risk-taking behavior, obsessive/compulsive behavior, sleep disturbances and unawareness. Irritability is the most frequently reported and is often accompanied by aggression (Nance et al., 1996; Pflanz et al., 1991), although undiagnosed psychiatric conditions such as depression, mania, or psychosis may be the underlying cause. Apathy, manifested as a loss of interest and concentration is also a commonly symptom experienced by both, HD individual and caregivers. In the studied cases, apathy appears simultaneously with the movement disorder, which spans various stages of the illness. Irritability and apathy form a well-recognized complex, which is the most typical psychological manifestation of HD (Pflanz et al., 1991). Depression is an important manifestation with less prevalence among HD patients, which could be mistaken with apathy. However, it has been shown that depression does not significantly correlate with apathy, on the contrary depression has been significantly correlated with anxiety and agitation (Slaugther et al., 2001; Levy et al., 1998). Disinhibition, impulsivity, and risk-taking behavior classify for symptoms of dysexecutive syndrome which are typically provided by informants or clinicians rather the HD patients (Anderson & Marder, 2001; Goh et al., 2018). In fact, unawareness or anosognosia, which is defined by the difficulty of the patient to recognize their deficits and their impact, can also be present and observe across the motor, cognitive, emotional, and physical domains of the disease (McCusker & Loy, 2014). A range of sleep and circadian abnormalities have been reported in HD. At middle stages, several HD patients frequently manifest sleep disturbances due to their movements, particularly before falling asleep (Kirkwood et al., 2001). Importantly, depression, anxiety, and irritability significantly correlate with increased likelihood of suicidal ideation (Hubers et al., 2013; Eddy et al., 2016; Mcgarry et al., 2019; Wetzel et al., 2011). Also, in a large cohort of HD patients it has been documented that a better neuropsychologic diagnose was significantly associated with a decrease in progressive functional decline (Marder et al., 2000). Moreover, several studies have consistently reported that psychiatric disturbances worsen quality of life (QOL) to a greater extent than motor symptoms of the disease (Helder et al., 2001; Ho et al., 2009; Ready et al., 2008). First signs of motor dysfunction include involuntary movements in the distal extremities such fingers and toes, and in facial muscles. Progressively, these signs become more proximal and axial abrupt involuntary movements identified as chorea (Cardoso, 2009; Roos, 2010). During the course of the disease, hyperkinetic movements as chorea progressively disappear, while hypokinetic movements become more prominent, with bradykinesia, akinesia, rigidity, dystonia, dysarthria (unclear articulation), and dysphagia (swallowing difficulty). Other motor features include gait abnormalities, abnormal saccades,

myoclonus and tics (Anderson, 2011; Ghosh & Tabrizi, 2018; Roos, 2010). The cognitive alterations usually begin with a subtle impairment of intellectual processes being detected decades before the onset of motor symptoms (Langbehn et al., 2007). There is a progressive worsening of cognitive disturbances including deficits in visuospatial memory, executive memory, attention, working memory and verbal learning which gradually progress into profound dementia at late stages of the disease (Anderson, 2011) (Figure 1).

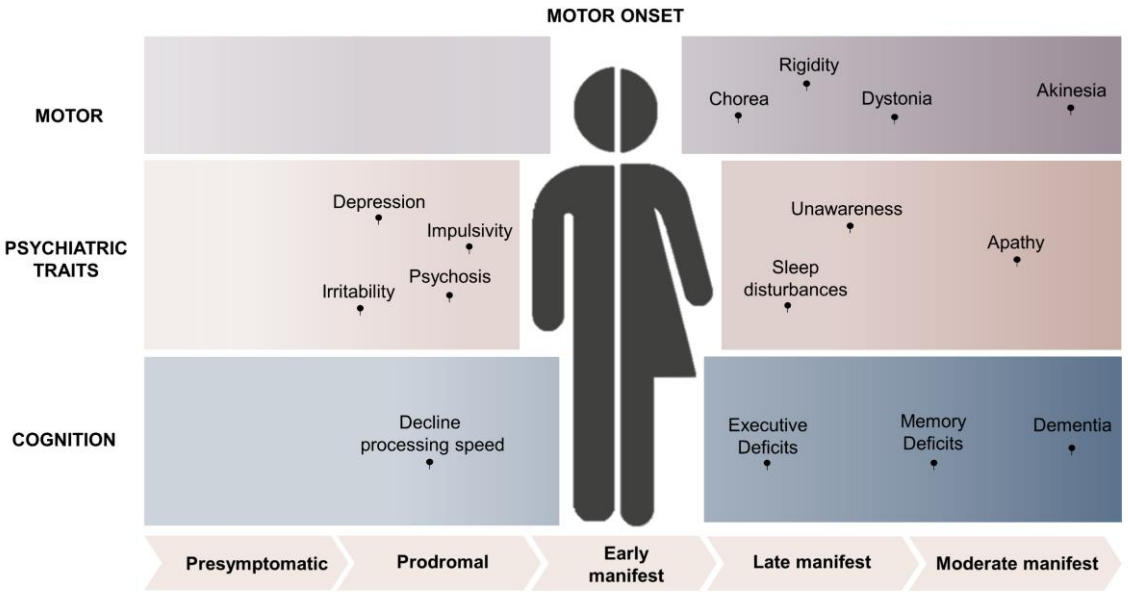


Figure 1. Clinical features progression in HD. Common clinical manifestations encompass a wide range of psychiatric, motor, and cognitive disturbances over the life span.

Advanced HD patients with substantial dementia and severe motor dysfunction may become unable to walk and they have poor dietary intake. Ultimately, they become unable to selfcare and more vulnerable to injuries as poor nutrition, infection, choking, and inflammation (Ghosh & Tabrizi, 2018; Novak & Tabrizi, 2010). Most HD patients die due to aspiration pneumonia because of swallowing difficulties, being the common cause of death in HD, while suicide is the second most common cause of death (Rodrigues et al., 2017; Schoenfeld et al., 1984; Solberg et al., 2018).

1.2. Genetics

HD is a monogenic autosomal dominant inherited disorder. In 1983, the genetic defect was first mapped to the short arm of the human chromosome 4p16.3 (Gusella et al., 1983). Years later, the causative mutation of the disease was described as an unstable expansion in the trinucleotide repeat formed by cysteine, adenosine, and guanine (CAG) in a newly described gene *IT15*. The *IT15* gene, later termed huntingtin *HTT* encodes for an undescribed protein of ~ 348 kDa, also named Htt (HDCRG, 1993). *HTT* is a large gene consist of 67 exons

spanning ~ 180 kb of genomic DNA (Ambrose et al., 1994), whereas (CAG)n mutation is in the exon 1.

In the normal population, the CAG trinucleotide normally repeats about 20 times, varying from 11 to 34 CAG copies (HDCRG, 1993; Duyao et al., 1993). A normal repeat, with less than 27 repeats, has never been associated with confirmed cases of HD (new mutation or sporadic cases) (ACMG/ASHG, 1998; Benjamin et al., 1994). An intermediate repeat, with 27 to 35 repeats, has not been associated with a HD diagnosis, but can be meiotically unstable in paternal transmission resulting in a risk of offspring inherited a HD allele with penetrance (Kremer et al., 1994; Chong et al., 1997; Goldberg et al., 1993). 36 to 39 repeats correspond with a reduced penetrance, that has been associated with the presence of the disease, but HD phenotype may not appear and occasionally individuals living beyond a normal like expectancy and do not develop any HD symptoms (Brinkman et al., 1997; Rubinsztein et al., 1996). A disease repeat, with 40 or more repeats, leads to a phenotype with full penetrance and HD pathology (Brinkman et al., 1997). Longer repeat sizes (>60) are usually associated with a juvenile HD presentation (Nance et al., 1999) (Figure 2).

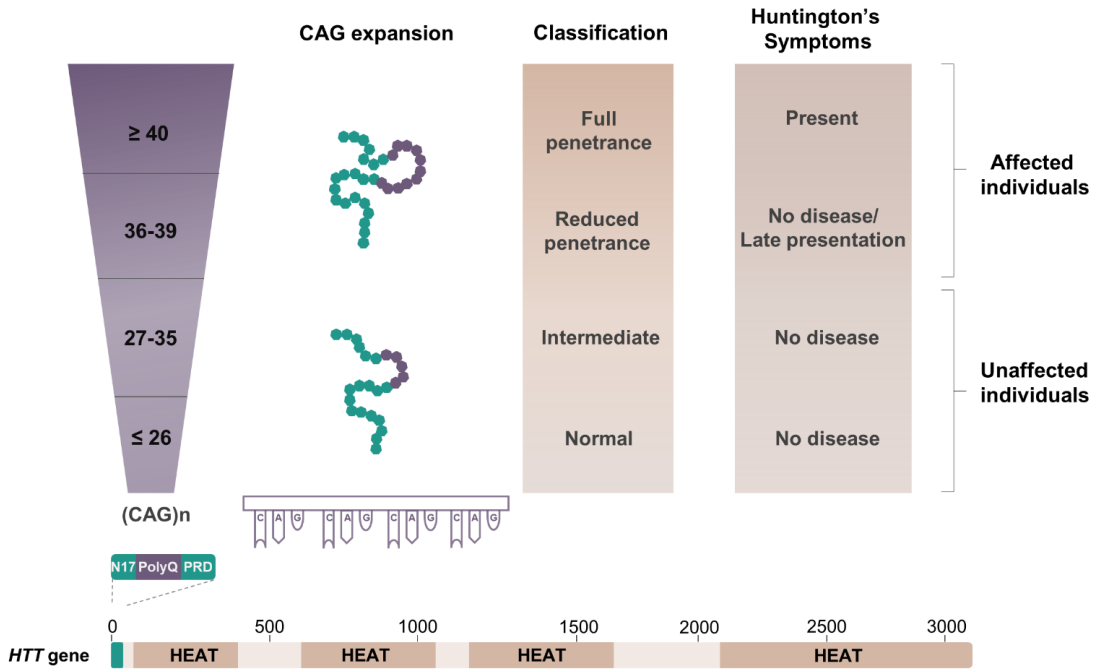


Figure 2. Diagram of *HTT* gene and CAG repeat length categories. Schematic representation of the aminoacidic (aa) sequence of *HTT* gene, including the polyglutamine (PolyQ), the proline-rich domain (PRD), and the HEAT domains. Boundaries indicate CAG repeat length which is closely related with penetrance of the disease in HD mutation carriers.

The instability of trinucleotide expansion in HD might explain the highly variable clinical expression, as exemplified by the high variability in age of onset. There is a strong inverse

relationship between age at onset and number of CAG repeats meaning that HD carrier mutations with longer CAG repeats commonly present an earlier age of onset (Brinkman et al., 1997; Duyao et al., 1993; Nance et al., 1999; Rubinsztein et al., 1996). Despite this robust correlation, CAG repeats size has shown to be a poor predictor of onset age, since the contribution of CAG length to age at onset can be subtle for cases with less than 52 repeats, which corresponds with most cases (Duyao et al., 1993). Thus, it has been estimated that residual variability in the age of onset might be due to other genetic and environmental factors (Wexler et al., 2004). Like other trinucleotide repeats disorders, CAG instability is linked to genetic anticipation, a phenomenon by which successive generations develop an earliest age-onset and a more severe phenotype. Greater size of repeat length is associated with male transmission, due to a particular instability of the CAG repeat during male gametogenesis such as most juvenile HD cases (Duyao et al., 1993; Ranen et al., 1995; Telenius et al., 1993; Trottier et al., 1994).

1.3. Huntingtin protein

Htt is large protein of ~ 348 kDa containing 3144 amino acids, and is highly conserved among vertebrates (HDCRG, 1993; Tartari et al., 2008). Htt is expressed ubiquitously throughout the body, predominantly in the brain and testes (DiFiglia et al., 1995; S. H. Li et al., 1993). In the brain, it is found in all type of neurons, as well as glial cells (Landwehrmeyer et al., 1995; Gutekunst et al., 1995; Hebb et al., 1999). Within the neurons, Htt is mainly found in the cytoplasm and colocalize with many organelles, including the nucleus, endoplasmic reticulum, Golgi complex, mitochondria, microtubules, endocytic and phagocytic vesicles, endosomes and synaptosomes (Gutekunst et al., 1995; Hoffner et al., 2002; Velier et al., 1998; Kegel et al., 2002; DiFiglia et al., 1995). Regarding to its structure, it has been described that Htt acquires the form of an elongated superhelical solenoid with a diameter of ~ 200 nm (Wei et al., 2006). Two important well-characterized features are the polyQ region, which is thought to mediate transcriptional regulation (Benn et al., 2008), and a series of HEAT (Huntingtin, Elongator factor3, PR65/A regulatory subunit of PP2A, and Tor1) repeats, which are 40-amino acid segments that mediate protein-protein interactions (Takano & Gusella, 2002; Andrade & Bork, 1995; Wei et al., 2006). Despite the gathered amount of information since the discovery, the physiological function of Htt protein is not entirely clear. Htt has shown to be essential for embryonic development since its absence resulted in embryonal death around day 8.5 (Nasir et al., 1995; Duyao et al., 1995), and to play an important role in preventing cellular apoptosis (Rigamonti et al., 2000; Zhang

et al., 2006), transcriptional regulation (Zuccato et al., 2003; Wu et al., 2010; Shimojo, 2008), vesicle trafficking and axonal transport (Pal et al., 2006; Caviston et al., 2007; Wu et al., 2010; Gauthier et al., 2004). Normal Htt seems to have a remarkable beneficial role in the brain, conversely in HD the presence of an aberrant expanded polyQ tract compromises cellular processes given place to pathological mechanism (Bates et al., 2015; Zuccato et al., 2010; Jiang et al., 2016; Jimenez-Sanchez et al., 2017; Ross & Tabrizi, 2011). It also seems that both, a gain of function of mHtt and to a lesser extent a loss of function of wild-type huntingtin underlie the neurobiochemical and neuropathological features of the disease (Zuccato et al., 2010). The deleterious effects of a gain of function of mHtt will be addressed in the following sections of this thesis.

1.4. Neuropathology

Regardless the ubiquitous expression of mHtt in somatic tissues, the pathologic features are seemingly restricted to the brain. Earliest major pathologic and biochemical changes are bounded to the striatum, a brain region which encompass the caudate and putamen in humans. Striatum along with the external segment of the globus pallidus (GPe) suffers a progressive neuronal loss and atrophy, in conjunction with astrogliosis that in the long-term results in the enlargement of the ventricular system. With the progression of the disease, the atrophy is widely and symmetrically spread throughout the brain showed by the 80% of HD brains atrophy involving mainly the frontal lobes in a rostro-caudal direction (Vonsattel et al., 2008, 2011). Progressive brain atrophy is already showed by premanifest and early HD patients, which also present progressive cortical volume loss, as well as white matter loss in the frontal lobe (Aylward et al., 2011; Tabrizi et al., 2011).

To study the evolution and severity of neuropathological changes in the HD striatum, and the relationship with clinicopathological features, the neuropathologist Jean Paul Vonsattel developed a grading system in 1985. Based on the macroscopic and microscopic features of striatal degeneration, 5 different grades (grades 0-4) were correlated with the chronological and topographical evolution and severity of HD striatum degeneration. Grade 0 corresponds with brains macroscopically unchanged, and an 30-40% loss of neurons in the head of the caudate nucleus. Grade 1 defines brains which tail and body of the caudate nucleus may show atrophy and neuronal loss, whereas head of caudate nucleus show a 50% reduction of neurons. Grade 2 is assigned to brains with mild to moderated gross striatal atrophy while Grade 3 designates brains with severe striatal atrophy. Grade 4 is designated when the

striatum is substantially atrophic with a 95% of neuronal loss (Vonsattel et al., 1985, 2011, 2008) (Figure 3).

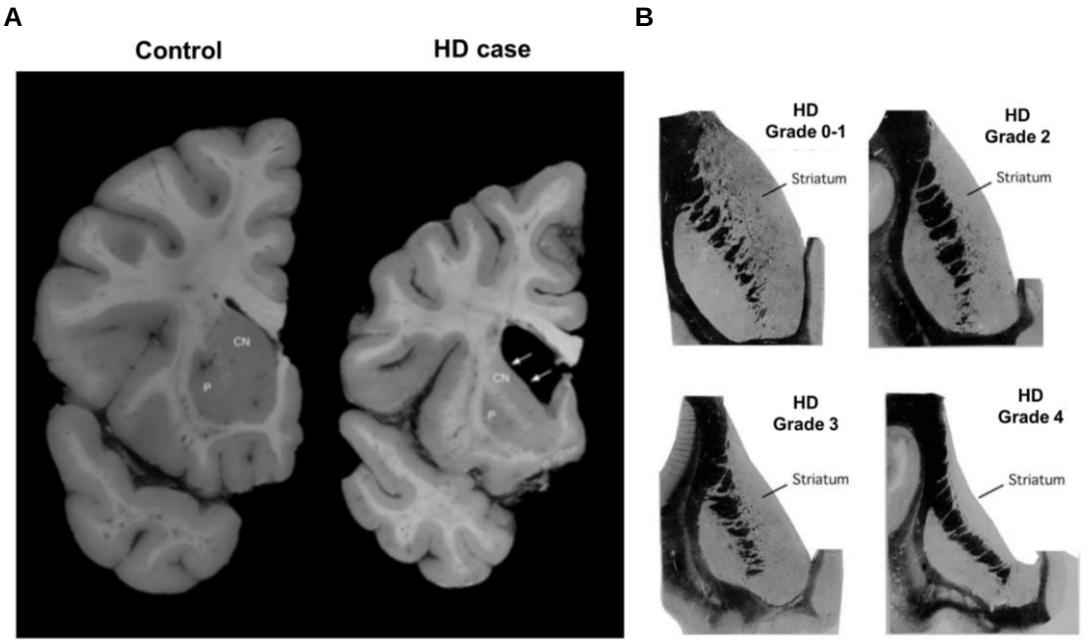


Figure 3. Neuropathological features in HD. (A) Human coronal brain sections from a control case (left) and an advanced HD patient (right). Dramatic atrophy of caudate (CN) and putamen (P) indicated by white arrows, along with cortical atrophy and enlargement of the lateral ventricle. Adapted from (Waldvogel et al., 2014). **(B)** Schematic illustrations showing the progression of macroscopic degeneration of the striatum indicated by Vonsattel grading system. Adapted from (Reiner et al., 2011).

Typically extrastriatal regions as cortex, thalamus, hippocampus, amygdala, subthalamic nucleus, substantia nigra, and cerebellum also show atrophy and neuronal loss. However, these findings are less consistent across investigations due variation of the degrees atrophy and neuronal loss depending on disease stage (Vonsattel et al., 2011). Regarding cortical changes, an important morphometric study of 81 HD prefrontal cortices reveals a loss of pyramidal neurons in layers III, V, and VI in grades 2–4, with the greatest loss in grade 4 (Sotrel et al., 1991). Following studies have extensively corroborated atrophy and volume loss in the several areas and layers of the HD mutation carrier cerebral cortex (Rüb et al., 2016). Degeneration of the thalamus of HD patients is described in some early neuropathological HD reports (Vonsattel et al., 1985; Vonsattel et al., 2008; Vonsattel and Difiglia, 1998; Walker, 2007). Recent studies describe those thalamic neuropathological changes are not only confined to cerebellar territory of the thalamus as the motor ventrolateral nucleus (Dom et al., 1976), but also occurs in the thalamic centromedian-parafascicular complex (CM-Pf), which projects to striatum, and in the mediodorsal nucleus which shows volume shrinkage, significant neuronal loss and astrogliosis (Heinsen

et al., 1999, 1996; Kasubek et al., 2005; Rüb et al., 2016). More recently, several attempts involving advanced neuroimaging studies of HD brains reveal changes in cerebral spinal fluid volumes and abnormal thinning of cortical sulci (Squiteri et al., 2009; Nopoulos et al., 2007), and confirmed regional cortical degeneration, whole brain atrophy, and significant loss of grey and white matter (Ciarmiello et al., 2006; Beglinger et al., 2005; Henley et al., 2009; Tabrizi et al., 2009). Neuropathological changes as progressive and region-specific atrophy of the brain has been recapitulated in several HD mouse models (Aggarwal et al., 2012; Crevier-Sorbo et al., 2020; Etxeberria-Rekalde et al., 2021; Steventon et al., 2016; Zhang et al., 2010), with selective striatal neuronal loss (Dodds et al., 2014; Slow et al., 2003), and astrogliosis to a lesser extent (Ferrante, 2009).

Importantly, the presence of prominent nuclear and cytoplasmic inclusions has been revealed by immunochemical analysis of HD brains becoming a major feature of the disease. These inclusions can be detected long before the neuronal loss and the onset of the symptoms, although are more widespread in the brains of patients with juvenile onset rather than adult-onset of symptoms (Davies et al., 1997; DiFiglia et al., 1997; Gomez-Tortosa et al., 2001; Sapp et al., 1999). The occurrence of nuclear inclusions and neuropil aggregates are also described in several HD mouse models, even though are more frequently in mice carrying the truncated m*Htt* (Reddy et al., 1998; Hodgson et al., 1999; Schilling et al., 1999; Slow et al., 2003).

1.5. HD mouse models

Over the years, several HD animal and cellular models have provided a great amount of knowledge about the key mechanisms underlying the pathophysiology of the disease and allowed the translation from basic research to clinical application. As the pathological hallmark of HD are the neuronal loss and degeneration of striatum, first animal models consisted of infusing excitotoxins into the rodent striatum to mimic the loss of striatal neurons (Beal et al., 1989). Administration of quinolinic acid (NMDAR agonist) (Beal et al., 1991; Schwarcz et al., 1983; Sanberg et al., 1989), kainic acid (kainate receptor agonist) (Coyle & Schwarcz, 1976; Divac et al., 1978; Mason & Fibiger, 1978) or mitochondrial toxin 3-niropropionic acid (complex II inhibitor of the mitochondrial respiratory chain) (Beal et al., 1993; Borlongan et al., 1997; Wüllner et al., 1994) remarkably mimic some HD biochemical (neuronal loss) and behavioral abnormalities (hyperkinesia). However, although excitotoxic models have shown to be reliable model for specific aspects of HD, they were unable to resemble the genetic origin of the disease and the deleterious and

progressive effect of mHtt widespread expression not only restricted to striatum (Ramaswamy et al., 2007).

The discovery of the mutation responsible for HD in 1983 allowed the development of accurate genetically engineered organism as models of the disease, including yeast, fruit flies, zebra fish as well as a wide range of mammalian models such as mouse, rat, sheep, pig, and non-human primates (Lelos & Dunnett, 2018). Among them, mouse models have been widely accepted due its similarity with the human genome, the animal small size, as well as the short generation time becoming a potential cost-efficient model (Vandamme, 2014). Genetic manipulations used in the development of genetic-modified mouse model of HD, first consisted of the targeted disruption of homologous HD gene (*Hdh*) in a mouse, generating a knock-out (KO) model. The null mouse model resulted in embryonic lethality, while heterozygotes mice for this mutation recapitulated some of the behavioral deficits and biochemical alterations in HD (Duyao et al., 1995; Nasir et al., 1995; Zeitlin et al., 1995). These results provide evidence of subtle consequences for a loss of function of Htt, suggesting that toxic function of mHtt is the major cause of the HD pathophysiology.

Subsequent approaches have been based in the random insertion of the expanded CAG tract into the mouse genome generating 3 different mouse model. Fragmented transgenic mice, which are inserted with a truncated fragment of m*HTT*, full-length mice, inserted with the entire m*HTT*, and knock-in (KI) models which are created by the insertion of the mutation in the mouse *Htt* locus. Within the fragmented models, the R6 mouse line was the first genetically engineered HD mouse model, created by the randomly insertion of the exon 1 of the human *HTT* gene. Two well characterized lines have been derived from these exon-1 mice, R6/1 and R6/2, that contains ~115 and ~145 CAG repeats respectively (Mangiarini et al., 1996). A few years later, the N171-82Q model was generated by the insertion of the first 171 amino acids of the human exon-1 with 82 CAG repeats under the prion promoter of the mice (Mangiarini et al., 1996). Regarding the full-length transgenic models, the researchers used a yeast artificial chromosome (YAC) or bacterial artificial chromosome (BAC) vector system to express the entire human *HTT* gene under control of the human *Htt* promoter. YAC128 mouse model expressing the human m*HTT* with 128 CAGs, is the most widely used among YAC mouse models (Hodgson et al., 1999). BACHD97 model expresses the whole human *HTT* with a mixture of 97 CAG/CAA repeats (Gray et al., 2008). KI models were created by the recombination of the human *HTT* gene with a chimeric human/mouse fragment containing different CAG repeat. HdhQ92, HdhQ111, CAG140

and zQ175 models are the most used (Menalled et al., 2003, 2012; Wheeler et al., 1999, 2000) (Table 1).

Table 1. Main genetic mouse models used in HD. Information about genetic manipulation, promoter type and CAG repeat length of each mouse model is provided.

MOUSE MODEL	GENETIC MANIPULATION	PROMOTER	CAG REPEAT LENGHT
	Fragmented transgenic mouse		
R6/1	Human *HTT* exon 1 randomly inserted (3 copies) into genome	Human *HTT*	116
R6/2	Human *HTT* exon 1 randomly inserted into genome	Human *HTT*	144
N171-82Q	Human *HTT* exon 1, 2, part of 3 (first 171 amino acids) randomly inserted into genome	Mouse prion protein	82
	Full-length transgenic mice		
YAC128	Full-length human *HTT* randomly inserted intro genome	Human *HTT*	128
BACHD	Full-length human *HTT* randomly inserted intro genome	Human *HTT*	97 (CAG/CAA mixtured)
	Knock-in mice		
HdhQ92	Endogenous *HTT* exon 1 replaced by chimeric human/mouse exon 1	Mouse *HTT*	92
HdhQ111	Endogenous *HTT* exon 1 replaced by chimeric human/mouse exon 1	Mouse *HTT*	111
CAG140	Endogenous *HTT* exon 1 replaced by chimeric human/mouse exon 1	Mouse *HTT*	140
zQ175	Endogenous *HTT* exon 1 replaced by chimeric human/mouse exon 1	Mouse *HTT*	175

Overall, HD mouse models recapitulate HD neuropathological, neurobiochemical and behavioral scenario, although fragmented transgenic models show an earlier and more severe phenotype due the length of the CAG repeats in the N-terminal, while KI present a delay in the appearance of the symptoms and pathologic features. Reduced lifespan and dramatic weight loss are common features in the fragmented R6/1 and R6/2, and the N171-82Q models (Mangiarini et al., 1996; Schilling et al., 1999). Lifespan is also shortened in full-length YAC128 model, but unaltered in the BACHD model, whereas both HD models have a gain of weight compared to WT controls (Gray et al., 2008; van Raamsdonk et al., 2005). KI models generally show a normal lifespan and body weight (Wheeler et al., 2000). Brain atrophy with substantial neuronal loss and neuronal mHtt inclusions are prominent features in full-length and fragmented mouse model, although R6/1 model experiences striatum shrinkage and BACHD shows degeneration in the absence of neuronal death (Gray et al., 2008; Hodgson et al., 1999; Mangiarini et al., 1996; McBride et al., 2006; Slow et al., 2003; Stack et al., 2005; van Dellen et al., 2000; van Raamsdonk et al., 2005). Conversely, even when KI mouse model shows early mHtt inclusions in the nucleus, brain atrophy and neuronal loss is rarely observed (Hickey et al., 2008; Hölter et al., 2013; Lin et al., 2001). Progressive cognitive and sensorimotor abnormalities have also been extensively documented in HD models. HD models typically show gait abnormalities and hindlimb clasping behavior (Hodgson et al., 1999; Mangiarini et al., 1996; McBride et al., 2006; Naver et al., 2003; Slow et al., 2003; Stack et al., 2005; Wheeler et al., 1999, 2000), although fragmented R6/1 and R6/2 mouse models also exhibit stereotypic involuntary grooming movements (Clifford et al., 2002; Mangiarini et al., 1996). Early hyperactivity of the locomotor behavior is also common in the R6/1, R6/2 and the YAC128 which progressively decline resulting in hypoactivity (Bolivar et al., 2004; Hodgson et al., 1999; Lüesse et al., 2001; Slow et al., 2003). Progressive motor impairment is also observed, although the onset and severity vary according to the penetrance of the disease between models (Hodgson et al., 1999; Lin et al., 2001; McBride et al., 2006; Menalled et al., 2003; Slow et al., 2003; Stack et al., 2005). Working and reference memory deficits become evident in spatial learning task as the Morris water maze and alternation in the T-maze, or the novel object recognition test (NORT) (Brito et al., 2014; Giralt et al., 2011; Harrison et al., 2013; Hickey et al., 2008; Lione et al., 1999; Raamsdonk et al., 2005; Suelves et al., 2017).

Psychiatric-like behavioral spectrum is a heterogeneous feature among HD models regarding onset and progression during the disease. Anxiety- and depressive-like phenotypes have been the most extensively examined by classical behavioral test. Most HD mouse models exhibit

anxiety-like behavior: increased anxiety-phenotype is exhibited by the R6/2 and YAC128 in the open field (Chiu et al., 2011; Ciamei & Morton, 2008), whereas the 12-week-old BACHD mice spend longer times in the dark box (Menalled et al., 2009), and CAG140 mice displayed a higher latent to enter the light compartment of the dark box (Hickey et al., 2008). Conversely, R6/1 displays similar levels of anxiety-like behavior than WT mice, that switch into less anxiety-like phenotype at 24-week-old (Naver et al., 2003). Depressive-like behavior has also been documented in several HD models, using the forced swimming test (FST), the sucrose preference, or the splash test which measure traits of depression as anhedonia, resignation, or apathy-like behavior. Most of the HD models subjected to the FST display a long duration of the immobility, suggesting a depressive-like phenotype (Chiu et al., 2011; Grote et al., 2005; Hickey et al., 2008; Orvoen et al., 2012; Peng et al., 2008; Pouladi et al., 2009; Renoir et al., 2011, 2012). YAC128 and R6/1 showed a lower preference for sucrose suggesting a depressive-like behavior, although in R6/1 mice this depressive behavior is sex-specific and exclusively displayed by female mice (Pouladi et al., 2009; Renoir et al., 2011). Similarly, reduced grooming frequency after a sucrose solution is described in female, but not male HdhQ111 mice, that can be interpreted as a loss of motivational behavior (Orvoen et al., 2012). A sex-specific component related to these behaviors become evident, HD females are more sensitive to develop depressive-like behaviors than HD males (Orvoen et al., 2012; Pang et al., 2009), whereas HD males are more likely to display anxiety-like behaviors than HD females (Hickey et al., 2005; Menalled et al., 2009; Orvoen et al., 2012). Even, when other traits of the psychiatric spectrum manifested by HD patients (irritability, impulsivity, sleep disturbances) are less investigated in mouse models, some studies have reported an abnormal social interaction in HD mouse models in the resident intruder paradigm. Early full-length models display significantly shorter latency in initiate a fight and more aggressive behavior towards the intruder, while R6/2 residents show a lack of interest for the intruder at late stages of the disease compared to WT mice (Shelbourne et al., 1999; Wood & Morton, 2015). Interestingly, two HD models experience a decline in circadian rhythms of activity and sleep suggested by a greatly decrease in the free running rhythms during constant darkness in the aged zQ175 mouse, and by a progressive age-dependent reduction in the total amount of wake during the dark period in the R6/2 mouse model (Kantor et al., 2013; Loh et al., 2013). Control deficits have been reported in the R6/2 mouse model, and in the tgHD rat model (Balci et al., 2009; Massioui et al., 2016). Remarkably, the BACHD mouse and the tgHD rat model have been subjected to the earliest quantifiable

behavioral assays since PND10 to PND21, showing decreased anxiety, increased risk-taking behavior and reduced emotionality (Siebzehnrübl et al., 2018).

Particularly, the R6/1 mice, the animal model used in this thesis, manifest a severe phenotype, with a delayed age onset and slower disease progression than R6/2 mice (Mangiarini et al., 1996). Hyperactivity in the open field at 4-week-old shifts to decreased spontaneous locomotor activity as disease progresses (Bolivar et al., 2004). First signs of motor impairment occur around 8-week-old, whereas severity of motor deficits increase over the weeks (Brooks et al., 2012; Hansson et al., 2001). Sensory-discrimination learning impairment has been reported at 10-week-old (Mazarakis et al., 2005). Cognitive alterations suggested by procedural memory deficits around 12-week-old appears prior to severe motor deficits (Cayzac et al., 2011; Giralt et al., 2011; Guiretti et al., 2016; Puigdellívol et al., 2015). Hindlimb clasping phenotype typically occurs around the 14-week-old, affecting less than the 40% of R6/1 mice (Naver et al., 2003). However, other studies report different number (Clifford et al., 2002), suggesting that clasping behavior test depends on the mouse colony. As previously referred, R6/1 mice exhibit less anxiety-like phenotype at late ages, while depressive behavior is sex-dependent and exclusively displayed by female mice (Naver et al., 2003a; Renoir et al., 2011) Histopathological findings describe striatal volume loss in the absence of neuronal loss at any age. MHtt cellular inclusions are first visible in the striatum at 8-week-old, and then spread to other region as their numbers increase with age (Hansson et al., 2001; Naver et al., 2003). Also, decreased dopamine and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein (DARPP-32) staining in the striatum beginning at 5 months of age (van Dellen, Welch, et al., 2000) indicates cellular dysfunction (Figure 4).

Although the R6/1 mouse model is a well-characterized HD mouse model regarding motor and cognitive behavioral features, the early/pre-symptomatic psychiatric spectrum has been poorly characterized. Therefore, in this thesis we aimed to examine the presence of early psychiatric traits around 4-week-old mice, since they have already been found in other HD rodent models.

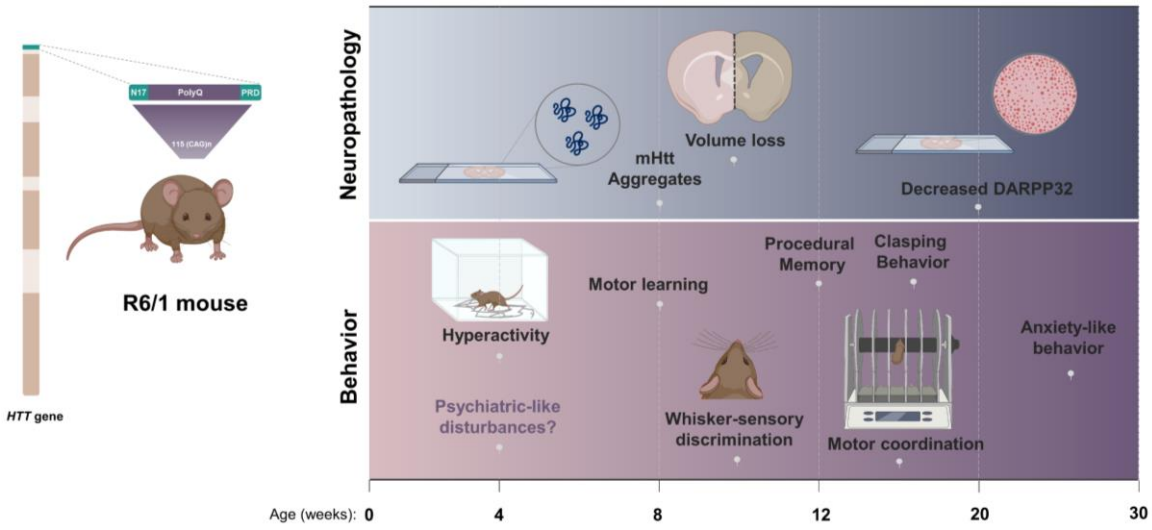


Figure 4. Timeline of behavioral deficits and neuropathologic features of the R6/1 mouse model used in this thesis. Schematic representation of motor, psychiatric and cognitive alterations accompanied by neuropathologic changes presented by the R6/1 mouse model along the weeks.

2. Molecular and cellular mechanisms involved in basal ganglia dysfunction

2.1. Basal ganglia dysfunction

The basal ganglia are involved in the origin and control of voluntary movement, as well as the determination of the movement sequence (Turner & Desmurget, 2010). The symptoms classically related with basal ganglia alterations are involuntary movements including tremor, chorea, ballism, athetosis and dystonia as well as muscular rigidity; hypotonia, disturbances in standing equilibrium, gait, speech, and akinesia (Yanagisawa, 2018). However, growing evidence reveals that basal ganglia circuit is involved in cognitive, associative, and emotional responses, and therefore, it plays a key role in cognitive disturbances and psychiatric disorders (Gunaydin & Kreitzer, 2016; Becker et al., 2016).

The striatum is the main input region of the basal ganglia. In humans, the striatum is formed by caudate nucleus, putamen, and ventral striatum, in which nucleus accumbens (NAcc) is included (Selden et al., 1994). The striatum receives massive glutamatergic and dopaminergic innervations. The excitatory glutamatergic input derives mainly from all regions of the cerebral cortex, as well as specific thalamic nuclei although to a lesser extent. The dopaminergic input comes from the substantia nigra pars compacta (SNpc) (Turner & Desmurget, 2010). Striatal neurons can be divided into medium-sized spiny projection neurons called medium spiny neurons (MSNs), and aspiny neurons. MSNs are GABAergic neurons that constitute 90-95% of the neuronal population in the striatum (Tepper et al., 2004). There are two major subtypes of striatal MSNs: Striatonigral MSNs, which predominantly express dopamine D1-like receptors and substance P, send their axons to the internal globus pallidus (GPi) and the substantia nigra reticulata (SNr), constituting the direct pathway. Striatopallidal MSNs, which preferentially express adenosine A2A-like or dopamine D2-like receptors and enkephalin, project to GPe which in turn projects to the subthalamic nucleus (STN) which projects to the GPi/SNr, constitute the indirect pathway (Shepherd, 2013). Aspiny neurons are less prone to degenerate than MSNs in HD.

Conversely, in HD at early stages striatopallidal MSNs are selectively loss, resulting in a disinhibition of the thalamus, that ultimately exerts an overactivation of the cortex causing hyperkinetic movements. Later, progressive loss of striatonigral MSNs induces the inhibition of the thalamus resulting in the appearance of hypokinetic symptoms of the disease (Albin et al., 1991; Reiner et al., 1988; Richfield et al., 1995) (Figure 5).

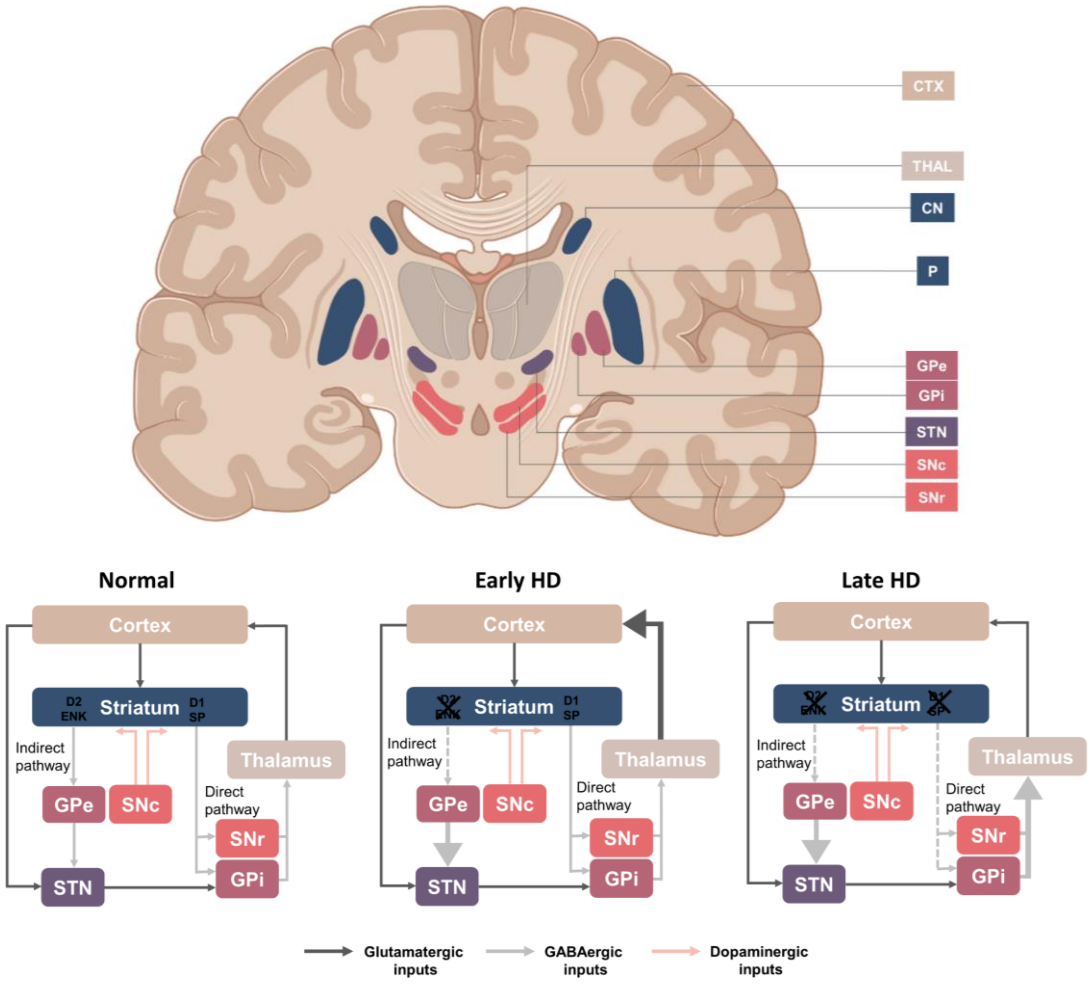


Figure 5. Basal ganglia circuitry in normal and HD pathological conditions. (A) Components of the cortico-basal ganglia loop in a coronal section of the human brain. **(B)** Schematic diagram of basal ganglia pathways in normal conditions, and in early and late stages of HD. Connectivity between regions are represented by arrows, weak connections (discontinued arrows) and strong connections (thicker arrows). CTX: cortex. THAL: Thalamus. CN: caudate nucleus. P: putamen. Gpe: external globus pallidus. Gpi: internal globus pallidus. STN: subthalamic nucleus. SNc: substantia nigra pars compacta. SNr: substantia nigra pars reticulata.

2.1.1. Intrastriatal circuit dysfunction

MSNs are the earliest and most severely affected neurons in HD neuropathology, displaying an initial and selective neurodegeneration until death (Cepeda et al., 2007). As mentioned above, there are two major subtypes of striatal MSNs: Striatonigral MSNs constitute the direct pathway and striatopallidal MSNs establish the indirect pathway (Shepherd, 2013). MSNs of the indirect pathway have been classically described as the most vulnerable and primarily affected neuronal population in the disease. At early stages of the disease, MSNs of indirect pathway experience a progressive and dramatic depletion of enkephalin in their fibber's projections to the external globus pallidus. At later stages in the disease, also MSNs of direct pathway exhibit a larger absence of substance P in their fibber's projections to

internal globus pallidus (Albin et al., 1991; Reiner et al., 1988; Richfield et al., 1995). Since these findings, it has been traditionally proposed that preferential cell loss of indirect pathway projecting to the external globus pallidus underlies motor symptoms of the initial clinical phase of HD, as hyperkinesia and loss of behavioural control. Cell loss of direct pathway leads to rigid-akinetic in the late clinical phase of the disease (Vonsattel & Difiglia, 1998).

Interneurons constitute a small fraction of the striatal neuronal population and result to be relatively spared during the disease progression (Reiner et al., 1988) except for parvalbumin interneurons, which are reduced in numbers in HD patients and the R6/2 mouse model (Giampà et al., 2009; Reiner et al., 2013; Reiner & Deng, 2018). Post-mortem HD brain tissues showed that neuropeptide Y-somatostatin neurons are spared or increased (Dawbarn et al., 1985; Ferrante et al., 1987) calretinin-positive interneurons are spared (Cicchetti et al., 1996; Ferrante et al., 1987; Massouh et al., 2008) as well as neurons containing enzyme acetylcholinesterase AChE-positive neurons which appear to be resistant to neurodegeneration (Ferrante et al., 1987) .

Electrophysiological studies in HD mouse model pinpoint that selective vulnerability of MSNs is due to intrinsic electrophysiological features. MSNs of R6/1 mouse model exhibit alterations in their membrane properties resulting in an abnormal excitability (Cepeda et al., 2007). MSNs of indirect pathway display greater alterations when compared to MSNs of direct pathway (Gertler et al., 2008), as shown by the occurrence of more action potentials (Kreitzer & Malenka, 2008), large membrane depolarizations and a reduced threshold to induce action potentials (Cepeda et al., 2008). Changes on active membrane properties could be explained by the fact that MSNs of indirect pathway are more selectively activated by cortical stimulation (Berretta et al., 1997), and there is also a preferential propagation of epileptiform activity onto MSNs D2-receptor neurons (Cepeda et al., 2008).

In vivo approaches using local field potential technique (LFP) propose a dysregulation of the neuronal activity patterns and their temporal dynamics in the striatum. Specifically, R6/1 and R6/2 mouse model show an increased individual neuronal firing rate, and a reduction coherent firing and bursting among pairs of neurons (Miller et al., 2011; Walker et al., 2008), suggesting that neuronal processing in striatum of symptomatic HD mouse models is compromised, not only at a single-neuron level, but also at a population level. Consistent with the previous results, electrophysiological recordings reveal that there is a significant decrease in synaptic connectivity between pairs of MSNs in R6/2 mice compared to WT littermates. These reduction in synaptic connectivity might be due to an increase of

GABAergic synaptic activity toward MSNs in R6/2 mice, particularly to MSNs of direct pathway. Both WT and R6/2 MSNs exhibit a feedback inhibition toward their pairs, but only R6/2 MNSs receive a strong feedforward inhibition generated by GABAergic interneurons (Cepeda et al., 2013). Indeed, GABAergic activity within striatum has been underlined as a potential source of increased inhibition and contributor of the silencing of MSNs. A consistent increase in the GABAergic current onto MSNs has been described in several mouse models. MSNs of R6/1 and R6/2 mice exhibit increased frequency of spontaneous GABA currents and increased IPSc. Particularly, R6/2 mice show these alterations since early stages and even present a particular subpopulation of MSNs that display higher GABAergic frequencies compared to WT controls (Cepeda et al., 2004).

GABAergic interneurons play an important role in striatal dysfunction in HD (Picconi et al., 2006), even when their role in the pathophysiology of the disease is not fully understood. In R6/2 and BACHD mice fast-spiking (FS) and parvalbumin-negative low-threshold spiking interneurons (pLTS) pairs show increased connectivity and higher firing responses to stimulation, standing out as another source of increased GABA transmission (Cepeda et al., 2013). Regarding glutamatergic transmission, GABAergic interneurons show reduced N-methyl-D-aspartate (NMDA) current (Cepeda et al., 2001), reduced density of NMDA receptors and different subunits composition compared with MSNs (Standaert, 1999). Additionally, it has been described that large interneurons are less responsive to all glutamate receptor agonists compared with MSNs (Calabresi et al., 1998). Altogether, these findings lead to theorize that sparing of large interneurons might be due to hyporesponsiveness to glutamate-containing input compared to striatal MSNs.

Also, electrophysiological recordings demonstrate the existence of a subset of MSNs with increased responsiveness to NMDA application at pre- and symptomatic stages and decreased responses to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at symptomatic stages (Cepeda et al., 2001; Levine et al., 1999). The increased response to NMDA accompanied by large glutamatergic synaptic events and increased Ca^{2+} concentration inside the cell underlie the basis of traditional excitotoxic hypothesis, which postulate that excitotoxic lesions in the striatum, generally produced by a selective activation of NMDA receptors in animals, induce effects similar to the neuropathological and neurochemical disturbances of HD (Beal et al., 1991; Bonfoco et al., 1995).

Enhancement of NMDA receptor function in MSNs have been widely reported in support of excitotoxicity hypothesis (Fan & Raymond, 2007). Moreover, it has been proposed a dual role for NMDA receptors based on the location of the receptor to synaptic or extrasynaptic

sites (Papadia & Hardingham, 2016). While synaptic NMDA receptors activate cellular survival pathways, on the contrary, extrasynaptic receptors activate pathways that lead to cell death (Levine et al., 2010). Additionally, electrophysiological experiments demonstrate increased extrasynaptic NMDA receptor-induced currents and signaling in a mouse model of HD providing robust evidence of a disruption in the balance between synaptic and extrasynaptic NMDA receptors (Milnerwood et al., 2010).

2.1.2. Corticostriatal dysfunction

Brain cortex is the main excitatory input to the striatum and plays a cardinal role in the early basal ganglia dysfunction in HD (Cepeda et al., 2003). Premanifest and early manifest HD patients have shown abnormal motor cortex excitability and synaptic plasticity (Orth et al., 2010; Schippling et al., 2009). Also, early reductions in visual and sensory-motor cortical functional connectivity have been reported in both pre-HD and manifest HD patients (Pini et al., 2020), which are consistent with visuomotor integration deficits (Say et al., 2011) and motor alterations (Ross et al., 2014). Neuroimaging analysis studies also identify functional connectivity abnormalities in the frontostriatal network in prodromal HD patients (Harrington et al., 2015), aberrant connectivity of lateral prefrontal networks (Wolf et al., 2008) and a decreased synchronous blood oxygen level-dependent (BOLD) activity between motor cortex and caudate nucleus confirming impaired corticostriatal functional connectivity since prodromal stages (Unschuld et al., 2012).

Several electrophysiological studies in HD mouse model have demonstrated changes in glutamatergic neurotransmission along the corticostriatal pathway, characterized by an early and transient dysregulation of glutamate release and progressive disruption of spontaneous synaptic currents (Cepeda et al., 2003; Joshi et al., 2009). In fact, studies have extensively reported that an excessive glutamate release by cortical projections could underlies MSNs NMDA-sensitization and subsequent excitotoxicity (Fan & Raymond, 2007; Heng et al., 2009; Shehadeh et al., 2006). Closely related to these findings, electrophysiological recordings show that cortical projections neurons in several HD mouse model display an elevated intrinsic excitability based on the changes in their membrane properties (Cummings, 2006; Cummings et al., 2009; Stern, 2011). Additionally, there is an increased excitatory drive to cortical projection neurons observed in several HD mouse models as YAC128, CAG140 and R6/2 mice (Cummings et al., 2009).

In vivo electrophysiological approaches have described a dysregulation in neuronal information processing and temporal dynamics in the medial prefrontal cortex. Overall, HD

mouse model have shown increased individual firing rates and temporally altered firing pattern suggested by decreased bursting and reduced synchrony between simultaneously recorded neurons (Miller et al., 2011; Walker et al., 2008). Using *in vivo* calcium imaging resolution that allows the study of large cell population at single-cell resolution, it has been confirmed an increased frequency of calcium transients in cortical neurons at the premanifest stage and at disease onset in transgenic and knock-in HD mice (Arnoux et al., 2018; Burgold et al., 2019; Donzis et al., 2020).

Looking more deeply onto the corticostriatal neurotransmission, glutamate, the excitatory amino acid released by cortical afferents plays a prominent, even controversial role in the remodeling of corticostriatal pathway in HD. First, classical excitotoxicity theories sustain that excessive activation of glutamate receptors lead to striatal degeneration (Fan & Raymond, 2007). Indeed, it has been demonstrated that excessive amounts of glutamate in the synapse could induce excitotoxicity and eventual neurodegeneration (Estrada-Sánchez et al., 2009). Also, striatal injection of glutamate-NMDA receptor agonists induces selective loss of striatal MSNs, accompanied with behavioral features of HD, in both rodents and non-human primates (Beal et al., 1991; Fan & Raymond, 2007). However, although several electrophysiological studies described an exacerbated glutamate release by cortical projections (Fan & Raymond, 2007; Heng et al., 2009; Shehadeh et al., 2006), microdialysis approaches provide less compelling evidence for glutamate as a contributor of excitotoxicity in HD. One study reported a substantial decrease of the striatal glutamate levels in 16-week-old R6/1 in basal conditions but enhanced glutamate release upon activation, suggesting the presence of a higher presynaptic reservoir of releasable glutamate or dysfunctional glutamate transporters (NicNiocaill et al., 2001).

More recent evidence proposes a lack of clearance or removal of glutamate from the synapse after its release showing a reduction of the expression of glial glutamate transporter-1 (GLT-1) in HD mouse model striatum compared to WT controls (Estrada-Sánchez et al., 2009; Estrada-Sánchez & Rebec, 2012). Similarly, excitatory amino acid transporter 2 (*EAAT2*) mRNA levels (the GLT-1 equivalent in humans) is also decreased in HD postmortem brain tissue (Arzberger et al., 1997) along with a deficient glutamate uptake (Hassel et al., 2008) (Figure 6).

Multimodal MRI *in vivo* studies show reduced glutamate/glutamine ratio in the striatum of HD mice at late stages (Fernández-García et al., 2020) and magnetic resonance spectroscopy performed in HD patients reports altered glutamate/glutamine and lactate levels, suggesting that combination of glutamatergic dysfunction along with alterations in energy metabolism

might work together promoting neuropathology in HD (Koroshetz et al., 1997; Taylor-Robinson et al., 1996).

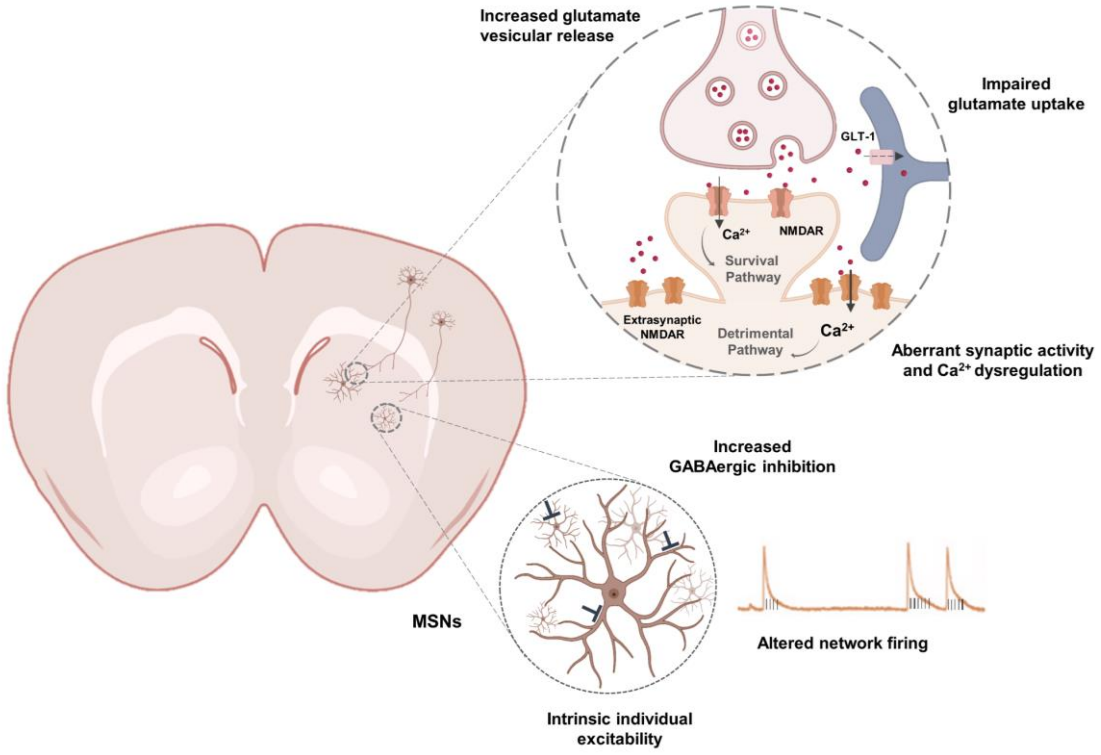


Figure 6. Corticostriatal dysregulation in HD at early stages. Cortical dysregulation comprises a wide range of presynaptic and post-synaptic alterations, together with intrastriatal disturbances are central mechanisms in the pathophysiology of the disease.

Corticostriatal disconnection comes along with a progressive loss of brain-derived neurotrophic factor (*Bdnf*) from cortex to striatum, promoted by a decline in cortical *Bdnf* gene transcription (Zuccato et al., 2001), and also by mHtt disruption of axonal transport of BDNF from cortex to striatum (Baquet et al., 2004). Absent of BDNF leads to a significant decrease in the number of striatal neurons compared to WT mice, decrease in soma area, dendrite thickness and dendritic spine density (Baquet et al., 2004). Also, disruption of BDNF through genetic manipulations or cortical deafferentation in mice could converge in reduced expression of neuronal markers in striatal neurons such as parvalbumin, calbindin, and the dopamine-regulated phosphoprotein DARPP-32 (Altar et al., 1997; Ivkovic et al., 1997; Jones et al., 1994). Importantly, it has been demonstrated that decline in BDNF levels advances the onset and severity of behavioral motor deficits in HD, and is closely related to a loss of MSNs D2-receptors (Canals et al., 2004). Additionally, studies have been described

autocrine and paracrine neuroprotective effects of BDNF in the survival of MSNs (Alberch et al., 2002). Also, neuroprotective effects of BDNF against excitotoxicity and oxidative insults in HD mouse models has been reported (Melo et al., 2013; Pérez-Navarro et al., 2000). Moreover, the normalization of BDNF levels reduces brain pathology, slows HD disease progression, and promotes survival of mutant mice (Duan et al., 2003; Giralt et al., 2011).

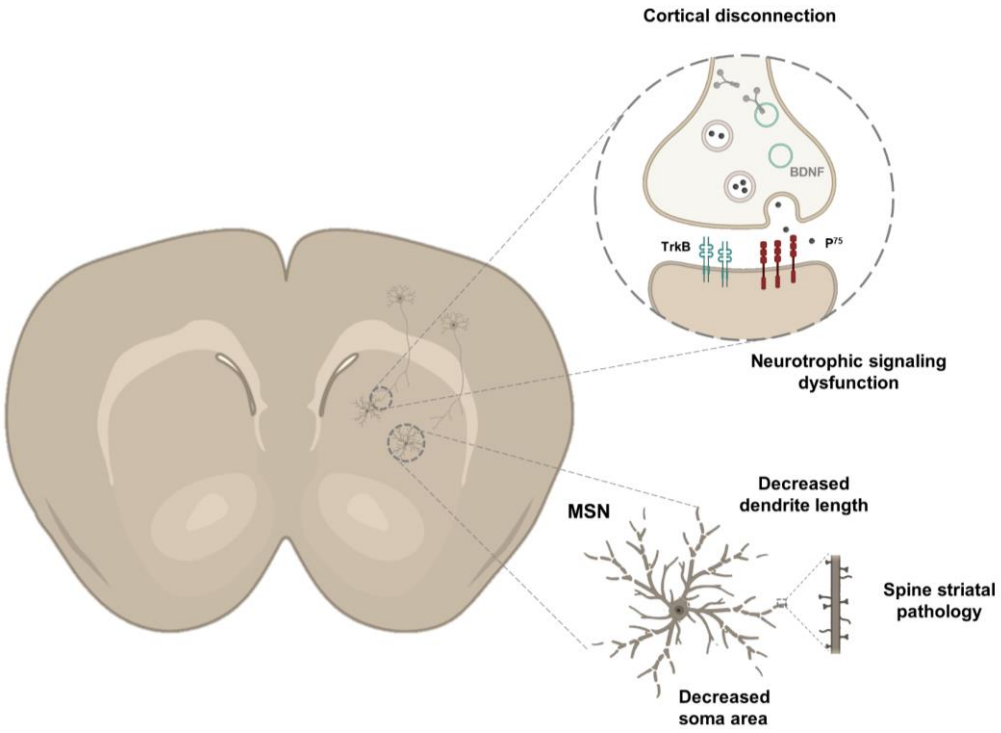


Figure 7. Corticostriatal dysregulation in HD at middle and late stages. Progressive cortical disconection with the disruption of BDNF trophic support leads to degeneration of MSNs population.

An imbalance between expression of BDNF receptors tropomyosin receptor kinase B and p75 neurotrophin receptor (TrkB/$p75^{NTR}$) has been described in HD patients and mouse models and linked to synaptic plasticity defects (Brito et al., 2014). *TrkB* mRNA and/or protein levels are markedly reduced in HD patients and mouse models (Simmons, 2017), whereas increased levels of $p75^{NTR}$ have been found in humans and mouse models (Brito et al., 2014; Zuccato et al., 2008). Even when the most contrasted hypothesis is that BDNF signaling through their receptors TrkB/$p75^{NTR}$, are responsible for the long survival or death of the entire populations of MSNs (Simmons, 2017), some studies have investigated to what extent downregulation or upregulation of BDNF receptors could contributing to the disease onset and progression. It has been reported that deletion of TrkB in MSNs of the indirect pathway results in hyperlocomotion, indicating that BDNF-TrkB signaling pathway in those

neurons controls the inhibition of motor behavior (Besusso et al., 2013). Conversely, an increase in the expression and signaling of the TrkB receptor has been related with an improvement of the symptoms in the HD (Brito et al., 2013, 2014). Moreover, normalization of $p75^{NTR}$ signaling improves HD-associated phenotypes in two HD mouse models (Brito et al., 2014; Simmons et al., 2016) (Figure 7).

Altogether, these data suggest that disturbances in the BDNF levels and receptors play an important role in the pathophysiology of MSNs from the onset of the disease, by directly affecting MSNs survival and function, particularly MSNs of the indirect pathway.

2.1.3. Nigrostriatal dysfunction

Traditionally it has been postulated that behavioral abnormalities in HD as hyperkinetic choreic movements in the early stages result from an initial dysfunction of the D2-enriched indirect pathway, while hypokinesia during the late stages is a consequence of an impairment in D1-enriched direct pathway. This knowledge arises from evidence of the involvement of the dopamine nigrostriatal pathway in HD pathophysiology. Concretely, previous studies have demonstrated an increase of dopamine levels in postmortem brains of HD patients and that dopamine-depleting agents, such as tetrabenazine (TBZ), could have a therapeutic benefit (Bird, 1980; Spokes, 1980).

For years biochemical studies found that the level of dopamine markers in autopsied HD brain striatum appear to be unchanged (Bernheimer et al., 1973; McGeer & McGeer, 1976) or increased (Bird, 1980; Spokes, 1980). However, later neurochemical studies of HD patients suggest that exacerbation of dopamine levels occurs in the early stages of the disease (Garrett & Soares-da-Silva, 1992) while levels of caudate dopamine and homovanillic acid, the principal dopaminergic metabolite are reduced in postmortem brains of late-stage HD patients (Kish et al., 1987). Thus, these last findings lead to conclude that dopamine levels in HD may show time-dependent changes associated with biphasic movement abnormalities suggesting that early dopaminergic increases are concomitant with chorea while late dopaminergic decreases occur during akinesia. Nevertheless, in animal models this view has been less consistent. Recent studies carried out in the YAC128 and BACHD show that in the early hyperkinetic stage MSNs of the direct pathway received more excitatory inputs than control animals, while MSNs of indirect pathway are not affected. In contrast, in the late hypokinetic stage both pathways receive less excitatory inputs compared to controls (André et al., 2011; Galvan et al., 2012). Also, even when at late stages of the disease dopamine release has been found decreased, consistent with dopamine disturbances in HD patients, R6/2 and YAC128 mice

commonly show a progressive reduction in striatal dopamine levels associated with motor abnormalities (Callahan & Abercrombie, 2011; Hickey et al., 2002; Johnson et al., 2006).

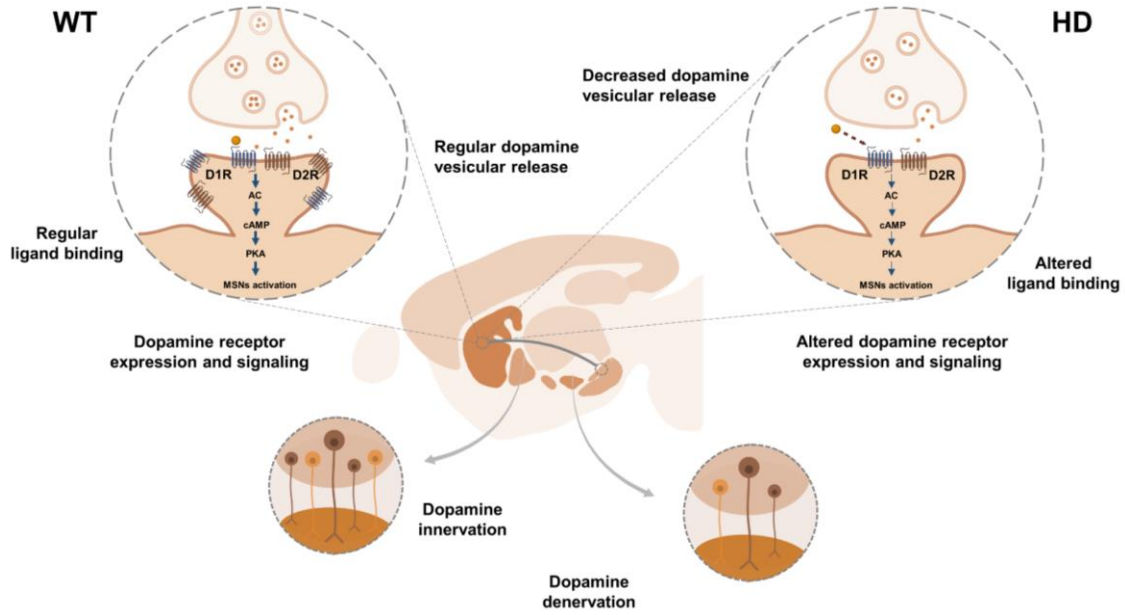


Figure 8. Nigrostriatal pathway in normal and HD pathological conditions. Progressive dopamine denervation from substantia nigra pars compacta is accompanied with altered dopamine receptor expression, deficiencies in ligand binding and dopamine signaling in MSNs.

Studies examining dopamine transporter (DAT) density involved in dopamine reuptake after release into the synapse and vesicular monoamine transporter type 2 (VMAT2), which is used to estimate the extent of dopaminergic innervation report that both are reduced in postmortem brain of HD patients (Bäckman et al., 1997; Ginovart et al., 1997; Suzuki et al., 2001). These data suggest that reductions in DAT levels correlate with a loss of dopaminergic nigrostriatal terminals, consistent with the view that the dystonic late-stage symptoms of HD may arise in part from critical reductions in dopaminergic transmission.
Other studies using positron emission tomography, autoradiography, markers for pre- and postsynaptic markers and imaging demonstrated that both, presymptomatic and symptomatic HD patients undergoes a reduction in striatal dopamine D1 and D2 receptor density, corroborating that dopamine signaling is disrupted early in HD (Joyce et al., 1988; van Oostrom et al., 2009; Richfield et al., 1991). In agreement with the findings, striatal dopamine D1-like and D2-like receptors levels have been also found affected in HD mouse models. Further, striatal D1-like and D2-like receptors binding are reduced at early stages, with deficiencies in dopamine signaling particularly seen in R6/2 mice (Ariano et al., 2002;

Bibb et al., 2000; Cha et al., 1998). Also, significant reductions have been observed in mRNA levels of *D1-like* and *D2-like* receptors in late stage of YAC128 mice, but not in BACHD mice (Pouladi et al., 2012) (Figure 8).

2.1.4. Thalamostriatal dysfunction

The thalamus constitutes the second main excitatory input to striatum, accounting for at least the 40% of excitatory terminals in the striatum (Deng et al., 2013; Lei et al., 2013). Classically, it has been described that a separate region of thalamus, the intralaminar nuclei consisted of the centromedian-parafascicular nuclear complex, sends glutamate input to both direct and indirect MSNs as well as striatal interneurons (Ding et al., 2010; Lapper & Bolam, 1992; Smith et al., 2014). More recently, some reports have shown that striatum receives glutamatergic inputs from other important thalamic nuclei as the ventral posterior nucleus (VP) which projects to dorsolateral striatum implicated in sensoriomotor learning consolidation, whereas centromedian-parafascicular nuclear complex projects to dorsomedial striatal which contributes to sensoriomotor learning acquisition (Díaz-Hernández et al., 2018), the posterior thalamic nucleus (POm) also projects to dorsolateral striatum processing preferentially stimulus-responses associations (Pan et al., 2010; Smith et al., 2012) (Figure 9).

Interestingly, the thalamostriatal pathway shows early changes in thalamostriatal afferent connectivity preceding MSNs neuropathology in a HD mouse model (Deng et al., 2013; Deng et al., 2014) suggesting that loss of thalamostriatal terminals could contribute to HD-associated deficits. *In vitro* co-cultured reports reveal that thalamostriatal synapses on MSNs are significantly altered from early stages in the YAC128 mouse model. Specifically, thalamostriatal afferents show major changes in active membrane properties compared to corticostriatal afferents, suggesting that thalamostriatal axons are affected earlier. Additionally, when thalamostriatal afferents are stimulated, MSNs respond with a decrease in EPSC frequency suggesting a reduction in synaptic connections (Kolodziejczyk & Raymond, 2016). MSNs of YAC128 and R6/2 mouse models of HD showed slower rise and decay times stimulation, indicating an altered excitability in synaptic AMPA and NMDA receptor in conjunction with an enhanced activation of extrasynaptic NMDA receptor. In addition, when thalamostriatal projections are stimulated, they exhibit an increased probability of vesicular release that might emerge as compensatory mechanism for the loss of thalamic inputs (Parievsky et al., 2017) (Figure 10).

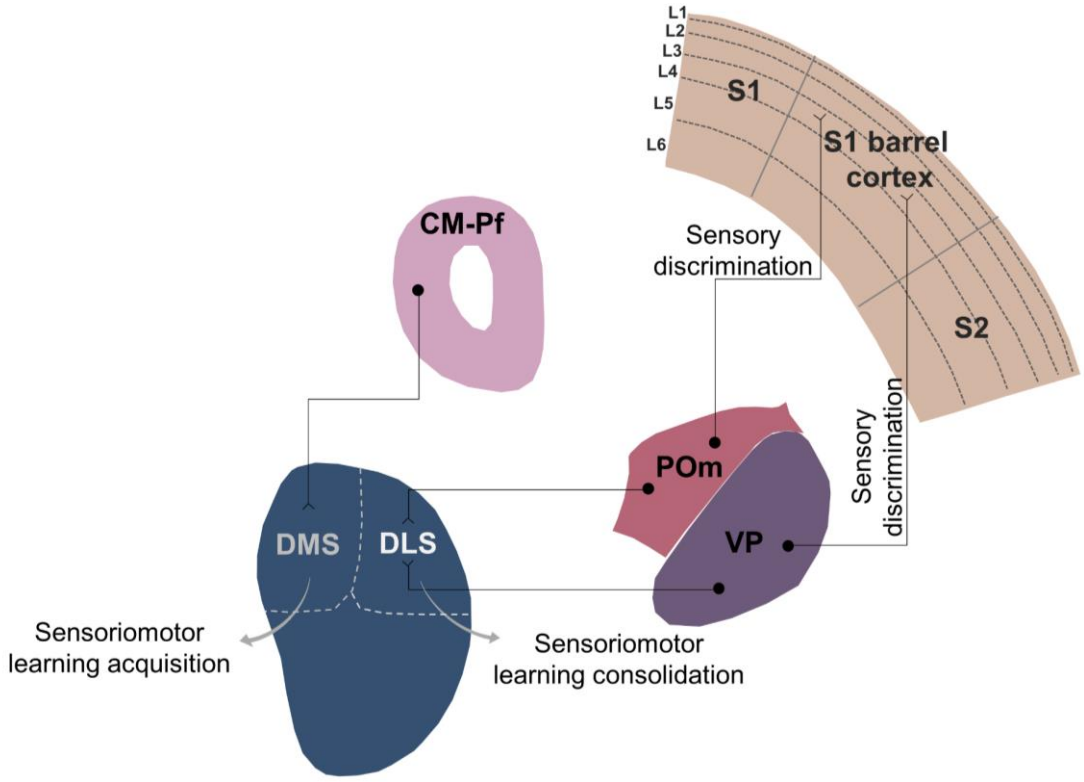


Figure 9. Main thalamic afferent pathways to striatum. Schematic representation of glutamatergic inputs from thalamus consisted of the centromediam-parafascicular nuclear complex (CM-Pf), the ventral posterior nucleus (VP) and the posterior thalamic nucleus (POm).

Some of the studies in the literature do not address thalamic dysfunction alterations in HD patients (Harris et al., 1996), or find a subtle decreased connectivity between a small part of the thalamus with the executive network in early clinical conditions of HD patients (Dumas et al., 2013). Interestingly, by using positron emission tomography a study has described an enhanced thalamic activation in preclinical HD subjects during the performance of a motor learning task (Feigin et al., 2006, 2007), a change that possibly emerges to compensate loss of corticostriatal activity in the very early preclinical period. Regardless, as disease progress this compensatory mechanism declines and the symptoms of HD begin to appear (Feigin et al., 2007). A resonance magnetic study evaluating energy metabolism in the thalamus of preclinical HD patients, describes metabolic thalamic changes such as reduction in aspartate levels (van Oostrom et al., 2007) that poorly correlated with CAG repeat length. These thalamic metabolic abnormalities in HD patients have been also confirmed by reductions of aspartate, glutamate, and choline levels (Casseb et al., 2013). Importantly, another metabolic study has provided evidence of reduced values in the concentration of aspartate and

creatinine levels in the thalamus of patients with HD, which show a correlation with the duration of disease (Ruocco et al., 2007).

Both, normal and pathologic function of thalamostriatal circuit have been relative neglected, the extent of the thalamostriatal dysregulation is still not fully understood in HD. Understanding thalamostriatal circuit alterations mediated by mHtt may be fundamental to have a broader perspective of the circuit alterations underlying the disease and decipher initial key mechanism of HD pathogenesis.

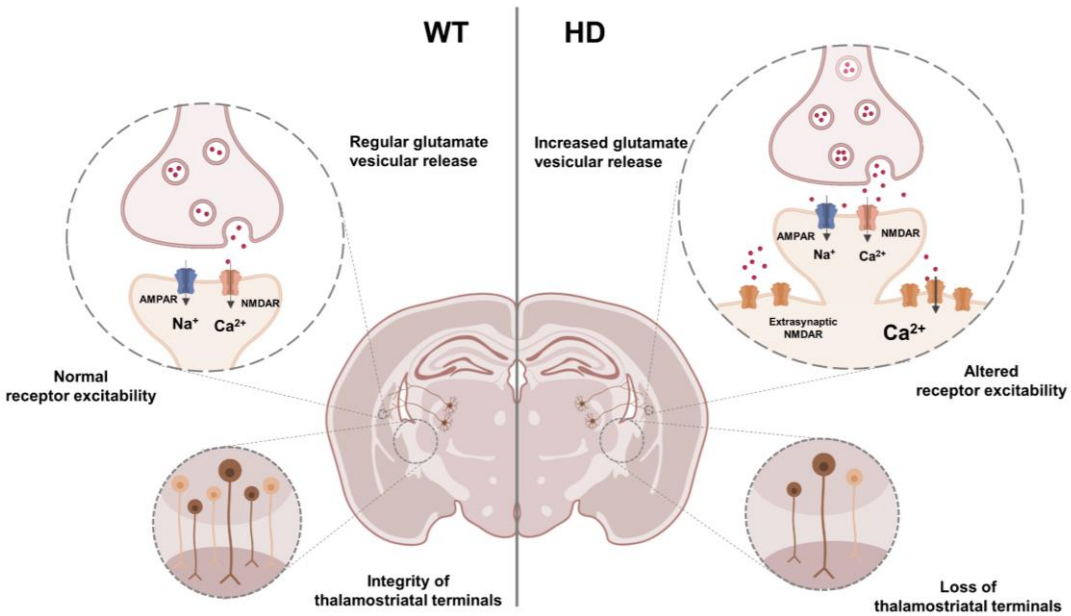


Figure 10. Thalamic afferent pathway in normal and HD pathological conditions. Loss of thalamostriatal terminals is concomitant with increase of glutamate release from thalamic terminals and postsynaptic alterations in striatal MSNs.

2.2. Synaptic Dysfunction

Long-term plasticity may occur at single synapses, manifested as a long-term potentiation or depression of synaptic efficacy, induced by changes in the pattern of synaptic stimulation, or may happen at a network level understood as homeostatic neuronal activity during a large period (Turrigiano, 2012). It appears to be that both types of long-term plasticity synaptic are severely affected in HD (Smith-Dijak et al., 2019).

Both, pre- and post-synaptic mechanisms contribute to enhanced excitatory input in HD mouse models (Cepeda et al., 2007; Plotkin & Surmeier, 2015; Raymond, 2017) (Figure 11). Studies trying to decipher HD pre-synaptic mechanisms have found that vesicular release is accelerated from HD cortical terminals in the striatum (Chen et al., 2018; Joshi et al., 2009) even when the number of functional cortical terminals is similar between the HD mouse

model and WT controls (Joshi et al., 2009). Likewise, vesicle release at the neuromuscular junction in R6/1 mice has been found to be accelerated (Valencia et al., 2013) suggesting that mHtt might interacts with synaptic vesicle release machinery. In that regard, it has been documented that voltage-gated N-type Ca^{2+} channel, which are essential for presynaptic neurotransmitter release (Zamponi, 2003), interacts with mHtt in a stage-dependent manner in the BACHD mouse model. These mHtt-protein interaction might result in biphasic dependent changes in the N-type Ca^{2+} channel cell surface expression and glutamate release (Silva et al., 2017). Interestingly, other two studies reveal the potential underlying mechanisms. A first study proposes a model predicting that an interaction between mHtt and syntanxin1A induces enhanced activation of N-type Ca^{2+} channel producing an increase in calcium influx and glutamate release (Swayne et al., 2005). A second study conducted in a Drosophila model of HD reports an increase in Ca^{2+} dependent neurotransmitter release, and a recovery to basal levels through a partial loss of function of N-type Ca^{2+} channel (Romero et al., 2008).

Likewise, induced-mHtt changes in presynaptic proteins involved in exocytosis and neurotransmitter release could underlie synaptic dysfunction in HD. For example, Complexin II that regulates membrane fusion between the synaptic vesicle and the presynaptic plasma membrane is reduced in HD patients (Morton et al., 2001), and in R6/2 mouse model, which becomes progressively depleted (Morton & Edwardson, 2001). Moreover, the phenotype caused by reduction of complexin II in the PC12 cell model can be partially reversed by overexpressing complexin II, which results in the normalization of neurotransmitter release from the PC12 cells (Edwardson et al., 2003) . Rabphilin 3A a small GTPbinding protein involved in priming and docking of vesicles to the plasma membrane is also decreased in HD patients (Morton et al., 2001) and in R6/1 mouse model. This decrease is progressive and concurs with the onset of symptoms (Smith et al., 2005). Rab3A knockout mice exhibit a mild phenotype, mainly characterized by impaired synaptic depression (Geppert et al., 1994) and long-term potentiation (Castillo et al., 1997). These last features resemble HD-associated synaptic deficits, which suggest that disruption in vesicle fusion machinery contributes to synaptic dysfunction in HD. Another relevant source that might be contributing to unregulated release of synaptic glutamate is the early loss of metabotropic glutamate receptor mGluR2 and dopamine D1-like receptors at corticostriatal synapses in the R6/2 mice, which activity regulates the appropriated vesicular glutamate release (Cha et al., 1998). Similarly early loss of presynaptic of dopamine D1-like receptors levels has been found in presymptomatic HD patients (Weeks et al., 1996). In both cases, this altered

expression of neurotransmitter receptors precedes clinical symptoms suggesting that this early dysregulation contributes to neuropathological changes in the disease.

MHtt has also been associated with proteins of the post-synaptic compartment. More precisely, it has been suggested that in physiological conditions normal Htt binds to PSD-95 and sequesters the scaffold protein, resulting in the inhibition of NMDA receptor activity (Parsons et al., 2014). Instead, in the presence of mHtt, the interaction between PSD-95 scaffold protein and normal Htt is impaired. Finally, it turns in the increasing of NMDA receptors number and activity in the membrane surface (Sun et al., 2001) and subsequent aberrant activity in HD mouse models. The aberrant activity of NMDA receptors might also be due to an imbalance of the proportion of NMDA-R1 and NMDA-R2A/B subunits composition of NMDA receptors in HD mouse model striatum (Ali & Levine, 2006; Benn et al., 2007; Cepeda et al., 2001) predisposing striatal neurons to excitotoxic damage (Zeron et al., 2002). In addition, it has been widely demonstrated that trafficking of NMDA receptors in striatal neurons might be also affected (Fan & Raymond, 2007) resulting in the imbalance between synaptic (pro-survival) and extrasynaptic (detrimental) NMDA receptors (Milnerwood et al., 2010; Okamoto et al., 2009). Specifically, a recent study describe that forward trafficking of NMDA-R2B to the surface membrane is accelerated as result of the enhancement of calpain and Striatal Enriched protein tyrosine Phosphatase (STEP) activity in synaptic compartments. Ultimately, this aberrant combination destabilizes NMDA-R2B at synapses and promotes lateral diffusion to extrasynaptic sites, suppressing survival signaling and promoting cell stress pathways (Gladding et al., 2012). Interestingly, another study has showed an increase of the surface expression of GluN3A-containing NMDA receptors in YAC128 striatal neurons, due to an altered interaction of mHtt with PACSIN, a trafficking chaperone for GluN3A. Remarkably, restoration of GluN3A levels in YAC128 striatum reverse HD-associated deficits as mHtt excitotoxity, dendritic spine loss and cognitive and motor dysfunction (Marco et al., 2013).

NMDA receptor-dependent long term synaptic plasticity has been mainly investigated in the hippocampus and the cortex of multiple HD mouse model (Dalbem et al., 2005; Hodgson et al., 1999; Picconi et al., 2006; Usdin et al., 1999). Systematically, long-term potentiation (LTP) is impaired at hippocampal synapses as the result of an aberrant NMDA receptor function, exacerbated short-term potentiation and reduction of paired pulse inhibition, which corroborate altered pre-synaptic transmission in HD mice (Hodgson et al., 1999; Usdin et al., 1999). Interestingly, a more recent report has shown that short-term synaptic

plasticity and LTP is impaired the R6/1 mouse model, and that the severity of this impairment correlates with the size of the CAG repeat. Even more, the deficits in LTP and short-term plasticity can be rescued with a dopamine D1-like receptor agonist (SKF38393) (Dallérac et al., 2011) suggesting that dopaminergic modulation of corticostriatal pathway in HD plays a key role in synaptic plasticity dysfunction.

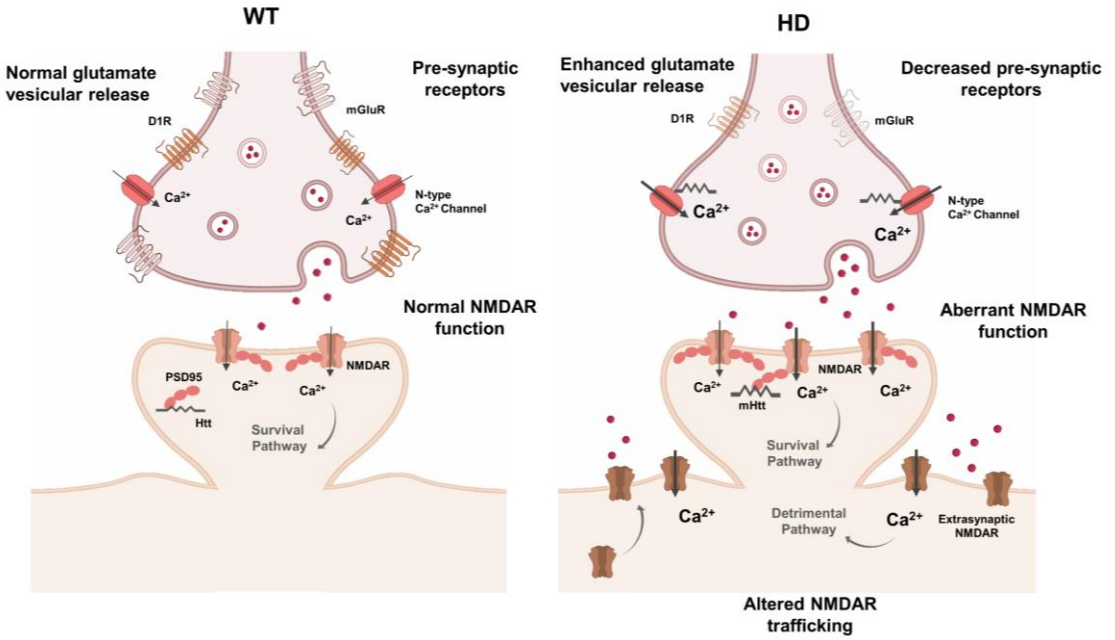


Figure 11. Mechanisms involved in enhanced excitatory synaptic activity in HD. Aberrant pre- and post-synaptic processes underlying synaptic dysfunction in HD.

In vivo electrophysiological study reports an altered Long-term depression (LTD) in the R6/1 mice model as well (Creus-Muncunill et al., 2019). Electrophysiological recordings in slices also describe that LTD is altered in corticostriatal synapses (Cummings et al., 2006; Ghiglieri et al., 2019) indicated by a loss of depotentiation after a train of low frequency stimulation (LFS). However, only one of the studies shows reversion of short and long-term abnormalities via dopaminergic modulation of dopamine D1-like receptor (Cummings et al., 2006).

Other synaptic alterations are observed in relation to cell micro-architecture. It has been suggested that synaptic disturbed mechanisms in HD could have a high impact on dendritic spine number and morphology, leading to spine loss and modification on spine volume and length and alterations in synaptic plasticity (Murmu et al., 2013). Several studies have found a decrease in dendritic spine density, smaller diameters of dendritic shafts and smaller dendritic area in R6/2 model mice (Klapstein et al., 2001). Similarly, it has been reported a

reduction of spine density in basal dendrites striatal neurons, as well as apical dendrites on cortical pyramidal neurons. Additionally, a decrease on the spine length of cortical pyramidal neurons has been found in a R6/1 mice model, as well as a decreased proportion of spines with branched morphology (Spires et al., 2004). In this mouse model, during the symptomatic stage of the disease, transient spines do not develop to persistent spines and a decrease in persistent spines is observed, meaning that new spine stabilization is impaired in R6/1 mice (Spires et al., 2004). Moreover, in human postmortem tissues, degenerative changes include truncated dendritic arbors, focal swelling in dendrites and accused spine loss (Ferrante et al., 1991; Graveland et al., 1985).

Thus, synaptic plasticity is severely altered in HD, comprising a widely range of disrupted mechanisms (reviewed in Smith et al., 2005), that ultimately converge into a profound lack of homeostatic neuronal activity and subsequent dysfunction of the whole HD network.

2.3. Transcriptional Dysregulation

Several cellular processes are involved in the pathogenesis of HD. For instant, mHtt affects the regulation of transcription factors, impairs mitochondrial energy pathways, increases the presence of aggregates that repress several proteins, affects vesicular organelle and neurotransmitter axonal trafficking, alters synaptic transmission and calcium homeostasis, and contributes to glial activation, endoplasmic reticulum stress, autophagy and proteosome activity deficits. From all these mechanisms, transcriptional dysregulation plays a fundamental role in the pathogenesis of HD, since occurs at early stages of the disease, and by affecting the expression of genes and proteins induces normal cellular processes turn into pathogenic mechanism as those mentioned before (Bates et al., 2015; Zuccato et al., 2010; Jiang et al., 2016; Jimenez-Sanchez et al., 2017; Ross & Tabrizi, 2011) (Figure 12).

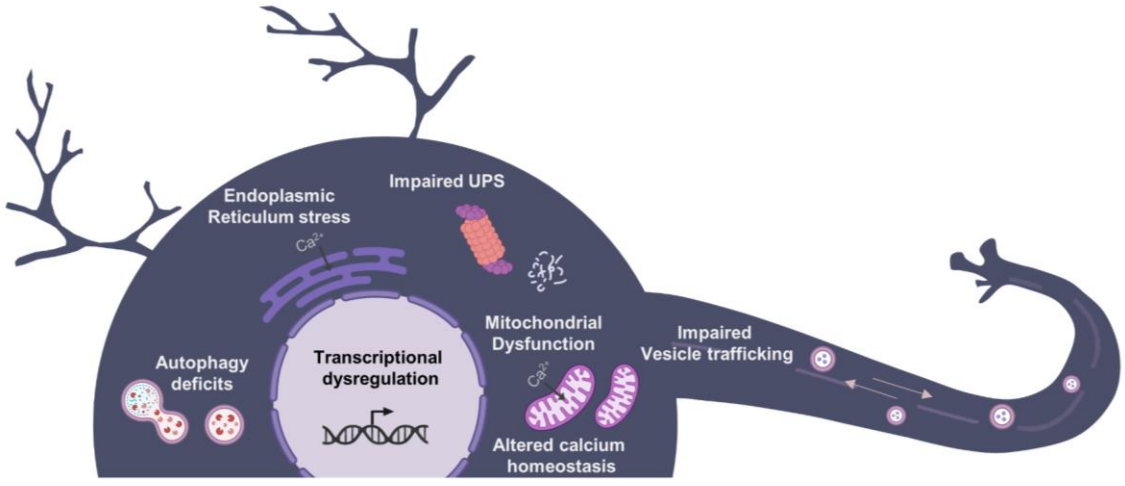


Figure 12. Key cellular pathogenic mechanism in HD. Deleterious effects of mHtt encompass a variety of aberrant cellular processes implicated in the pathogenesis of the disease.

The first evidence suggesting transcriptional dysregulation in HD has been provided from *in situ* hybridization studies on postmortem human HD brains. Specifically, expression of enkephalin, substance P, dopamine D1 and D2 receptor mRNAs have been found altered in the postmortem caudate-putamen tissue of early-grade HD patients (Augood et al., 1996, 1997). In agreement with these findings, first gene expression studies performed in the R6/2 mouse model corroborate a downregulation in the mRNA levels of several neurotransmitter receptors, in some cases, as the dopamine *D1-like* receptor or the metabotropic glutamate receptor *mGluR*, prior to onset of clinical symptoms (Cha et al., 1998). Later, cDNA microarray carried out on genetically engineered HD mouse models provided a global genomic view of the different groups of genes altered at different stages of the diseases. This analysis allowed the identification of several dysregulated mRNA associated with transcriptional processes, neurotransmitter receptors, synaptic transmission, cytoskeletal and structural proteins, intracellular signaling, and calcium homeostasis (Chan et al., 2002; Luthi-Carter et al., 2002; Desplats et al., 2006; Sipione et al., 2002).

Remarkably, more than 81% of striatal-enriched genes have been found decreased in the HD mouse model, and similar results have been observed in a subset of striatal genes in the caudate of HD patients (Desplats et al., 2006). Studies commonly describe a prevalence of downregulated transcripts over upregulated ones, particularly at early stages, corroborating that transcriptional dysregulation is an early and a progressive mechanism in HD (Gallardo-Orihuela et al., 2019; Luthi-Carter et al., 2000; Sipione et al., 2002; Wyttenbach et al., 2001).

Also, mRNA profiling analyses have shown that mutant mice expressing the longer or full-length transgene show fewer transcriptional changes compared with those expressing the short N-terminal fragments, suggesting that mHtt protein length may influences the ability of an expanded polyglutamine domain to alter gene expression, and that short N-terminal fragments of mHtt, rather than full-length mHtt, are those contributing to transcriptional dysregulation (Chan et al., 2002).

2.3.1. Mechanisms of transcriptional dysregulation

Although the exact processes leading to transcriptional abnormalities in HD are not fully elucidated, some of the potential mechanisms underlying these alterations have been

proposed. These mechanisms require an abnormal interaction between mHtt and key components of gene expression regulation leading to epigenetic-chromatin deregulation and dysregulation of the activity of several transcription factors.

First, acetylation and deacetylation of histones play a critical role in gene expression through the interaction of histone acetyltransferases (HATs) and histone deacetyltransferases (HDACs). In normal conditions, HATs activity induce an increase in gene transcription through the opening of chromatin architecture by adding acetyl groups. Conversely, HDACs remove acetyl groups leading to gene chromatin condensation (Verdin & Ott, 2014). Moreover, in HD there is an imbalance towards deacetylation and formation of condensed inactive heterochromatin that represses the transcription of different genes (Bassi et al., 2017; Valor & Guiretti, 2014). There are several deacetylases such as Sirtuin (SIRT) that is normally blocked by the normal Htt. Instead, in HD mHtt induces its overexpression, and in turn several transcription factors are repressed or blocked (Neo & Tang, 2018). For example, SIRT1 modulates transcription factors related with BDNF and mitochondrial function. Brain-specific KO of Sirt1 exacerbates brain pathology of HD mice whereas overexpression of SIRT1 improves survival, BDNF expression, significantly improves motor function, reduces brain atrophy, and attenuates mutant Htt-mediated metabolic abnormalities in HD mouse models (Jeong et al., 2011; Jiang et al., 2011).

Traditionally it has been postulated that mHtt drived by polyQs fragments aggregates into insoluble forms sequestering essential proteins, such as transcription factors (Nucifora et al., 2001; Steffan et al., 2000, 2001). However, this theory has been questioned since recent findings suggested that functional dysregulation of transcription factors precedes inclusion bodies formation (Schaffar et al., 2004; Mitra et al., 2009). Some studies have suggested that polyglutamine inclusions may sequester polyglutamine-containing transcription factors and deplete their concentration in the nucleus, leading to altered gene expression (Nucifora et al., 2001; Perez et al., 1998). On the contrary, other studies have shown a lack of colocalization between Htt aggregates and polyglutamine-containing transcription factor in HD mice, suggesting that altered gene expression likely results from the interaction between nuclear transcription factors and soluble mHtt, rather than sequestration by nuclear inclusions (Dunah et al., 2002; Yu et al., 2002). The presence of mHtt may lead to a dysregulation of transcription factors by the repression of their activity (Zuccato et al., 2010), or by the contrary facilitating an abnormal and pathological interaction with other proteins. Nevertheless, dysregulation of transcription during the disease may also be a consequence of

the loss of function of normal huntingtin resulting in a reduced interaction between Htt and transcription factors (Pogoda et al., 2020) (Figure 13).

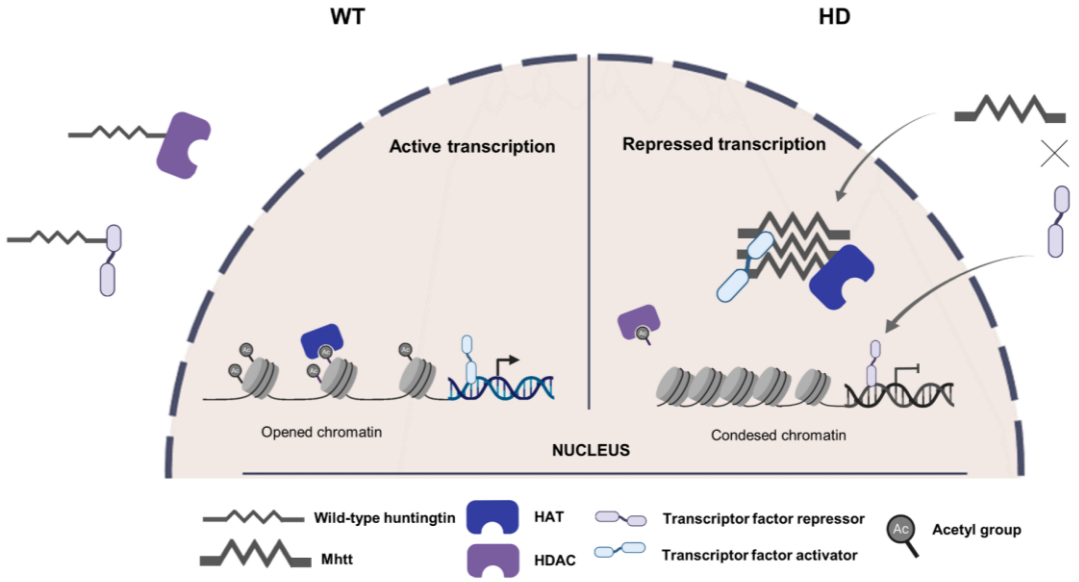


Figure 13. Mechanisms of transcriptional dysregulation in HD. MHtt may disrupts normal transcriptional activity by enhancing the interaction or sequestering activator transcription factor into the aggregates and eventually repressing gene expression, or facilitates the activity of repressor transcription factor by losing its interaction allowing them to get into the nucleus and represses transcription. MHtt can also interacts and alters the status of the histone acetyltransferases (HATs) and histone deacetylases (HDACs) inducing the chromatin structure to a more condensed state that ultimately causing repression of the transcription.

Among the extensive list of dysregulated transcripts in HD, RE1-silencing transcription factor, also known as neuron-restrictive silencer factor (REST/NRSF) and cAMP-response element CREB-binding protein (*Cbp*) are the most largely studied. In normal conditions, Htt interacts with REST/NRSF preventing the translocation into the nucleus and subsequent repressive activity upon target genes. In HD, mHtt lead to a loss of this normal interaction, REST/NRSF is accumulated in the nucleus and downregulates the expression of neurotrophins and their receptors such as BDNF and TrkB, and other many synaptic proteins contributing to the pathogenesis of HD (Shimojo, 2008). *Cbp* is a transcriptional coactivator that enhances CREB-mediated transcription of specific genes (Chrivia et al., 1993; Kwok et al., 1994). M*Htt* can interacts with *Cbp* through the glutamine-rich activation domain affecting transcription and gene expression or interact with the acetyltransferase domain of *Cbp* causing a reduction in histone acetylation and leading to gene repression through chromatin condensation, which resulted in a reduction of mRNA levels (Steffan et al., 2000; Steffan et al., 2001).

A relevant group that begins to receive special attention in the context of HD is the forkhead box (Fox) transcription factor family. Their structure allows DNA binding capacity and transcriptional activity, and it seems to perform a central role in regulating the expression of genes related to cell growth until brain development (Golson & Kaestner, 2016). Recently, it has been suggested that two members of the family, Foxp1 and Foxp2, interact with mHtt resulting in the downregulation of their levels and the decrease of their transcriptional activity. Particularly, reduced expression of Foxp1 in the striatum of humans and HD mouse models results in a loss of the genes related to the immune response, while reduced expression of Foxp2 can induce behavioral phenotypes associated with HD (Hachigian et al., 2017; Louis et al., 2017). Moreover, the overexpression of Foxp2 can alleviate these phenotypes, probably by restoring synaptic function (Hachigian et al., 2017).

Despite the gathered information described by Hachigian et al., 2017, the role of Foxp2 in HD has been poorly addressed and only in very advanced stages of the disease. In the next sections we will explain the role of Foxp2 in the central nervous system to understand and figure out to what extent Foxp2 could have a potential role in the pathogenesis of HD.

3. Foxp2 as novel therapeutic target in HD network dysfunction

3.1. *FOXP2* discovery

FOXP2 has been first associated with a speech and language disorder in the large KE family (Lai et al., 2001). Affected individuals have a severe impairment of the selection and sequencing of fine orofacial movements, which are necessary for articulation. The core deficit appears to be in the coordination of orofacial movements which is reflected in a relative immobility of the lower face and mouth of affected individuals (Vargha-Khadem et al., 1998). There are also deficits in language skills (Gopnik & Crago, 1991; Vargha-Khadem et al., 1995). Structural studies have shown abnormalities in several brain areas, including a bilateral reduction in the volume of the caudate nucleus thought to be the underlying pathological cause of the orofacial dyspraxia (Vargha-Khadem et al., 1998).

3.2. *FOXP2* structure, localization, and partners

The initial report of *FOXP2* described 19 exons, two of which (3a and 3b) are alternatively spliced into 4 different transcripts, covering approximately 300 kb on chromosome 7q31 (Lai et al., 2001). Later, it was suggested alternate splice variants and 5 others untranslated exons, a translated exon (4a) between exons 4 and 5, and a longer version of exon 10 (10+) that contains an alternate stop codon and produces a truncated protein (FOXP2-S). Later, one additional exon was identified in the intron 1. Thus, *FOXP2* consist of 25 exons, with 18 translated exons that spans approximately 600 kb of genomic DNA (Bruce & Margolis, 2002; Schroeder & Myers, 2008).

FOXP2 belongs to a family of transcription factors (Kaestner et al., 2000) called FOX proteins implicated in the regulation of cell growth and differentiation as well as embryogenesis and longevity (Carlsson & Mahlapuu, 2002). *FOXP (FOXP1–4)* is a newly defined subfamily of the FOX transcription factors which contains several recognizable sequence motifs, including a glutamine-rich region, a zinc finger, a leucine zipper, and a highly conserved forkhead domain (Lai et al., 2001; Shu et al., 2001). Unlike most other FOX transcription factors, members of the *FOXP* subfamily typically repress rather than activate transcription (Li et al., 2004).

The forkhead domain has a three-dimensional structure consisting of two Wl and W2 loops (or wings) and three α helices, whereas the α third helix allows the DNA binding (Katoh & Katoh, 2004; J. Li et al., 2021). *FOXP2* also contains two polyglutamine tracts, near to the N- terminal of the protein, consisting of 40 consecutive glutamines and 10 consecutive

glutamines becoming one of the longest polyglutamine stretches in the human genome (Lai et al., 2001). Leucine zipper motif is responsible for heterotypic and homotypic interactions among the *FOXP2* and other family *FOXP* members which is necessary for the regulation of its transcriptional activity. The zinc finger motif of *FOXP2* also regulates transcription activity. Finally, a highly acidic region at the C terminus, termed 'the acid-rich tail' contains the nuclear localization signals (NLSs) (Mizutani et al., 2007; Thulo et al., 2021) (Figure 14).

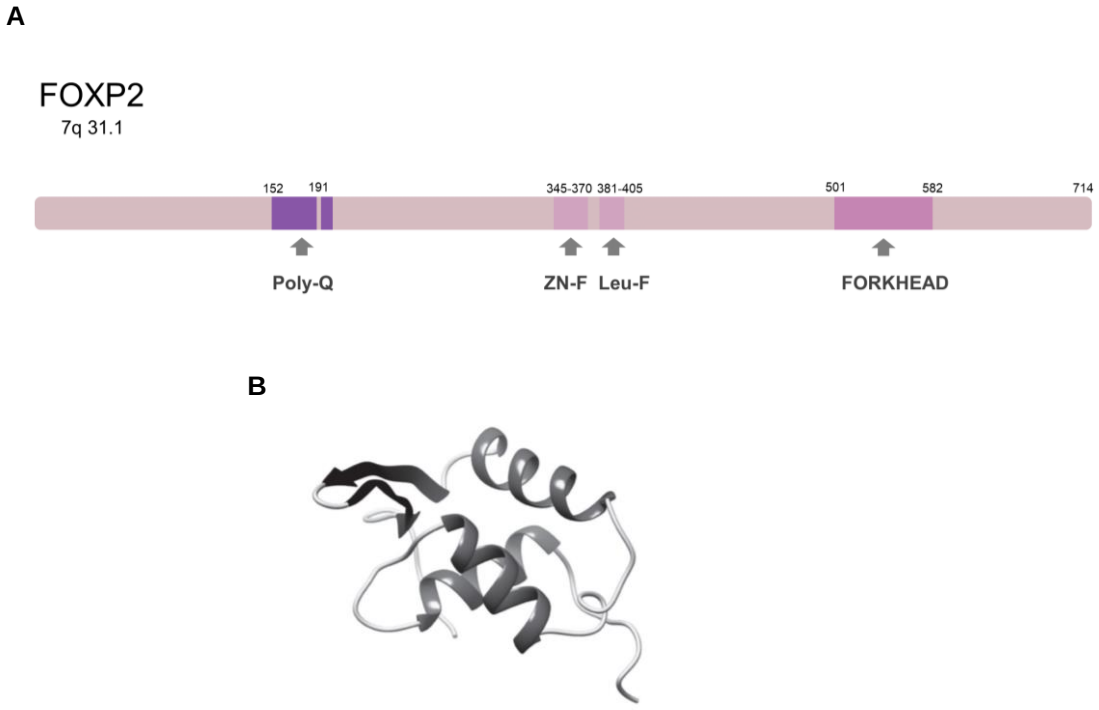


Figure 14. Human *FOXP2* gene and protein. (A) Representation of structural and functional domains of human FOXP2 protein. Poly-Q sequence, Zn finger, Leucine zipper and Forkhead domain are represented (arrows). **(B)** 3D structure prediction of the FOXP2 protein, which presents three α-helixes and two β-sheets. Adapted from (Castro Martínez et al., 2019).

FOXP2 is expressed at high levels in neural, lung and gut tissues during embryogenesis and adult life (Lai et al., 2003; Lu et al., 2002; Shu et al., 2001). Particularly, brains of human, mouse and rat show a highly expression of *FOXP2* since embryogenesis (Lai et al., 2003; Takahashi et al., 2003; Ferland et al., 2003; Teramitsu et al., 2004). In the mouse brain, *Foxp2* is mainly expressed in the neurons of the striatum, thalamus, cortical plate, and cerebellum having an important role in early development of central nervous system (Ferland et al., 2003; Vernes et al., 2011). *FOXP2* is crucial not only during embryogenesis, but it is also important in postnatal brain. Accordingly its expression is maintained throughout the entire lifespan in mice (Ferland et al., 2003) (Figure 15).

The exact function of *FOXP2* in the brain is not fully understood yet. In an attempt for unravel its potential role in the context of brain function and disease, several studies have documented relevant putative neural target and potential pathways. Out of the hundreds of putative targets (genes) of *FOXP2*, a small subset has received special attention through validation and follow-up in animal or cell-based models (Figure 16). One of the first genes to be extensively studied as a *FOXP2* downstream target has been the Contactin Associated Protein 2 (*CNTNAP2*), which encodes Caspr2, a neurexin transmembrane protein widely expressed in the brain implicated in nervous conduction, neuronal migration, neurite outgrowth, and connectivity (Rodenas-Cuadrado et al., 2013). *FOXP2* directly binds to regulatory motifs of the *CNTNAP2* locus to repress its expression (Adam et al., 2017; Mendoza & Scharff, 2017; SC et al., 2008). Interestingly, reported changes in *CNTNAP2* expression has been linked with developmental language and neurodevelopmental disorder, and also a range of brain-related phenotypes, including autism, schizophrenia and epilepsy (Alarcón et al., 2008; Bakkloglu et al., 2008; Friedman et al., 2007; Vernes et al., 2008; Strauss et al., 2009; Zweier et al., 2009).

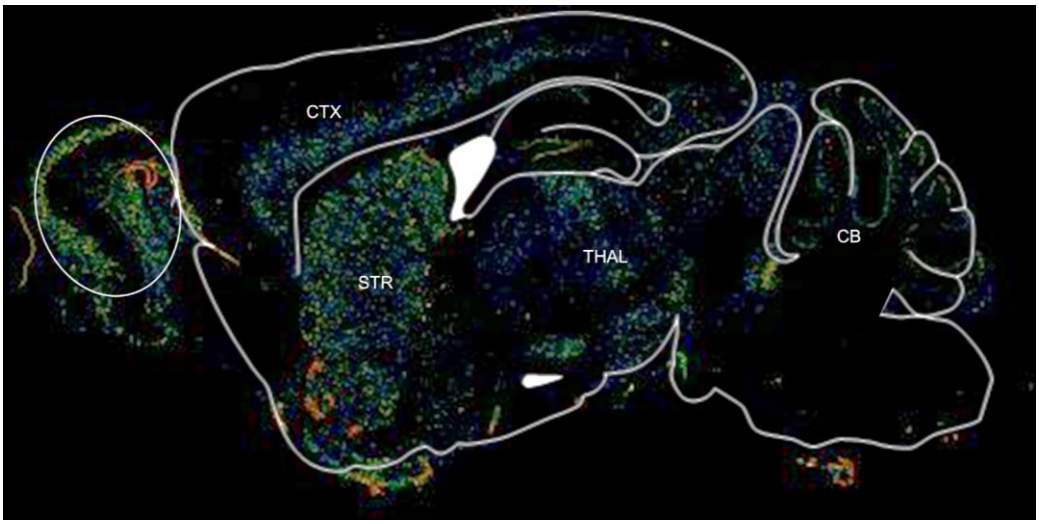


Figure 15. Localization of Foxp2 by in situ hybridization in the adult mouse brain. Intense hybridization signal is detected in the olfactory bulb, deep layers of the cortex, striatum, and to a lesser extent in thalamus and cerebellum in the coronal section of a brain mouse. CTX: cortex. STR: striatum. THAL: thalamus. CB: cerebellum. Adapted from Allen Brain Atlas.

Similar studies have identified others downstream genes repressed by *FOXP2* such as MET Proto-Oncogene, Receptor Tyrosine Kinase (*MET*) (Mukamel et al., 2011) and the Disrupted in Schizophrenia 1 (*DISC1*) (Walker et al., 2012; Spiteri et al., 2007). *MET* is a gene belonging to the tyrosine kinase receptor family (Zhang et al., 2018). It has been shown that common variation in *MET* has been associated with autism spectrum disorder and

schizophrenia (Burdick et al., 2010; Campbell et al., 2006). Also, post-mortem brain studies have shown altered *MET* expression in individuals with autism (Campbell et al., 2007).

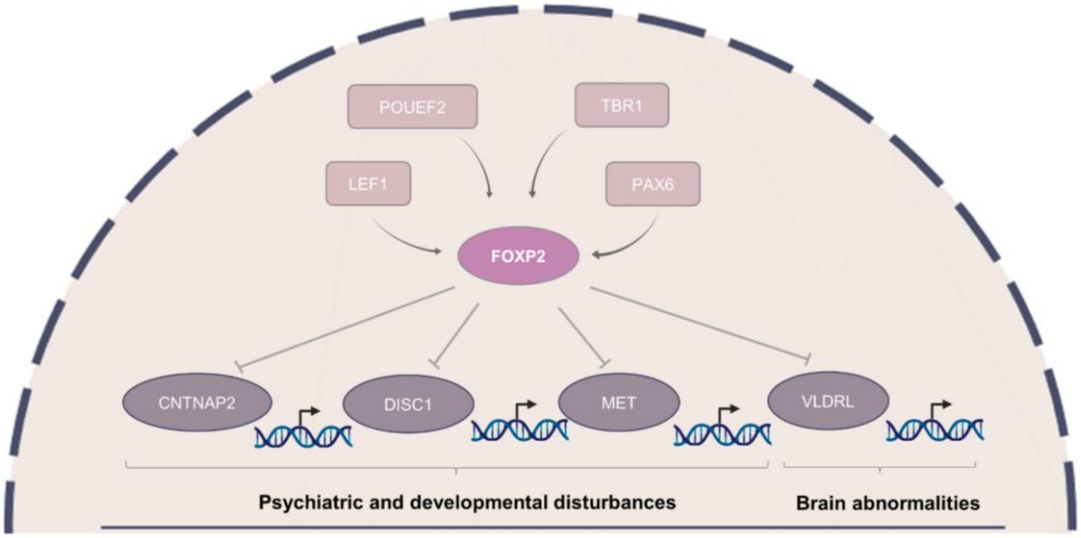


Figure 16. Molecular networks of Foxp2 in the brain. Subset of upstream and downstream target genes of Foxp2 and their implications in brain disorders.

DISC1 gene has also been related to schizophrenia (Brandon et al., 2009; Dahoun et al., 2017; Hodgkinson et al., 2004). Also, disruption in the *DISC1* locus segregates with bipolar disorder and recurrent major depression (St Clair et al., 1990). Even when *FOXP2* acts mainly as a transcriptional repressor, also has been reported to be a direct activator of very-low-density-lipoprotein receptor gene (*VLDLR*) (Adam et al., 2016; Mendoza & Scharff, 2017). Vldlr is a receptor for Reelin, expressed in the distal processes of migrating neurons in the developing cortex that regulates neuronal migration, and regulates dendrite and spine development (Chai et al., 2015; Niu et al., 2008). Homozygous deletion of the human *VLDLR* gene has been discovered in patients with cerebellar hypoplasia in which the normal cerebellar folia is missing (Boycott et al., 2005; Ozcelik et al., 2008).

Regarding the upstream chain, *FOXP2* locus contains six highly conserved binding regions for T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors, which are regulatory proteins that are activated by canonical WNT/β-catenin signaling (Bonkowsky et al., 2008; Richter et al., 2021). Among the TCF/LEF transcription is the lymphoid enhancer binding factor 1 (*LEF1*) which regulates *FOXP2* expression in vivo, corroborating in silico predictions (Bonkowsky et al., 2008). The *FOXP2* locus also includes highly conserved binding sites for Paired Box 6 (*PAX6*), a key regulator of central nervous system development. It has been described an absence of Foxp2 expression in the telencephalon of mouse embryos carrying a Pax6 null mutation while knockdown of Pax6 in developing

zebrafish embryos disrupts Foxp2 expression (Coutinho et al., 2011). *Pax6* mostly regulates migration and neuronal differentiation (Osumi, 2001). *POU3F2*, a well-known neural transcription factor also seems to regulate and increases *FOXP2* expression through an intronic regulatory element in the middle of *FOXP2* locus (Maricic et al., 2013). *Pou3f2* plays a key role in the formation and radial migration of upper-layer cortical neurons and facilitates the differentiation of glutamatergic neurons (Dominguez et al., 2013; McEvilly et al., 2002). *TRB1* constitutes another potential candidate which may regulates *FOXP2* expression. *FOXP2* and *TBR1* interact with each other and may co-regulate target genes in a cooperative manner (Deriziotis et al., 2014). In the cortex of Tbr1 knock-out mice the expression of Foxp2 is significantly decreased in the caudal area of layer VI (Siavash et al., 2018). In mice cortex, *Tbr1* is essential for development, guidance, morphology, and cortical neurons survival (Hevner et al., 2001).

3.3. Implications of Foxp2 in brain disorders

As previously mentioned, *FOXP2* was the first gene associated with speech and language disorder in the large KE family (Lai et al., 2001). Affected family members carried a heterozygous missense mutation (R553H) disrupting *FOXP2* and suffers a severe developmental verbal apraxia with impairment in both expressive and receptive language skills (Gopnik & Crago, 1991; Vargha-Khadem et al., 1995; Vargha-Khadem et al., 1998). Later on, new cases of *FOXP2*-related speech and language disorders, inherited and *de novo*, have been described. *FOXP2* mutation carriers exhibit a severe developmental verbal dyspraxia (DVD), also called childhood apraxia of speech (CAS) mainly characterized by difficulties in coordinating sequences of articulatory movements (MacDermont et al., 2005; Feuk et al., 2006; Reuter et al., 2017), and occasionally is accompanied for other alterations as global developmental delays, autism features and facial dysmorphology (Feuk et al., 2006; Morgan et al., 2017; Reuter et al., 2017).

Additionally, through the past two decades since the discovery, studies have investigated contributions of common variation in *FOXP2* among the population. Multiple studies confirmed that single nucleotide polymorphisms (SNPs) in the *FOXP2* gene are associated with schizophrenia risk (Tolosa et al., 2010; T. Li et al., 2013; X. Li et al., 2009; Liégeois et al., 2003; Rao et al., 2017; Sanjuán et al., 2006; Španiel et al., 2011), suggesting that *FOXP2* gene polymorphisms may confer vulnerability to schizophrenia. Large-scale systematic genome-wide association studies (GWAS) have identified significant associations of intronic *FOXP2* SNPs with several traits, including attention-deficit/hyperactivity disorder

(ADHD) (Demontis et al., 2019; Soler Artigas et al., 2019), risk-taking behaviors (Clifton et al., 2018; Strawbridge et al., 2018), major depression and major depression-related symptoms (Lane et al., 2017; T. Li et al., 2013). Collectively, these insights suggest a major role of *FOXP2* in neuropsychiatric disorders (Khanzada et al., 2017).

Finally, *FOXP2* also has been recently linked with HD as revealed by the substantial reduction of FOXP2 levels in postmortem brain striatum of individuals with stage III/IV HD and R6/2 mice. Additionally, the recovery of Foxp2 levels in the striatum of BACHD mouse model restores their motor coordination deficits (Hachigian et al., 2017).

3.4. Role of Foxp2 in the remodeling of synaptic plasticity and circuits

Foxp2 is known to be involved in synapse formation and synaptic plasticity (Rhijn et al., 2018), neurite outgrowth (Vernes et al., 2011) and neurogenesis (Tsui et al., 2013), being then, particularly important for brain development (Figure 17).

As disruptions of *FOXP2* gene in humans resulted in speech and language deficits, following studies has been focused in unraveling the potential roles of its orthologues through genetic manipulations in an array of animal models. The genetic manipulation of Foxp2 has been mostly oriented to the study to ultrasonic vocalizations in mice and birds. Foxp2 KO mice resulted in severe motor impairment, developmental delay, absence of ultrasonic vocalizations and premature death (Shu et al., 2005). Additionally, heterozygous Foxp2 mice also produced shorter sequences of ultrasonic vocalizations with less complex syntax (Chabout et al., 2016). These results has been consistently corroborated in knockdown and overexpression studies in the brains of zebra finches suggesting that Foxp2 acts as a regulator of vocal learning during development and also in the maintenance of vocal behaviors in adulthood (Day et al., 2019; Heston & White, 2015; Norton et al., 2019; Haesler et al., 2004; Xiao et al., 2021).

In addition to its role in language skills, Foxp2 is also important for the acquisition and performance of sequenced motor patterns. Mice carrying a missense mutation equivalent to the point mutation in KE family exhibit impaired motor-skill learning (French et al., 2012; Groszer et al., 2008). In line with the previous results, it has been described that Foxp2 conditional homozygous knockout targeting mouse cortex, striatum and cerebellum result in

a variety of motor-skill deficits suggesting that Foxp2 modulates different aspects of motor function (French et al., 2018).

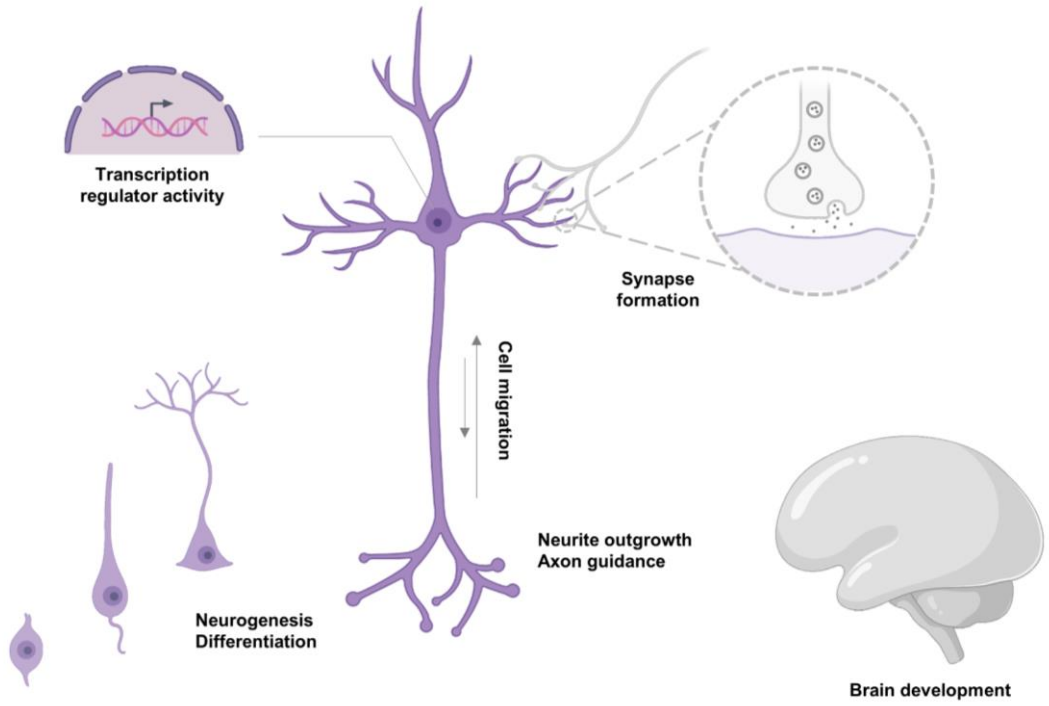


Figure 17. Overview of Foxp2 functions in the rodent brain. Schematic diagram showing the main cellular functions of Foxp2 in the mouse brain.

Along with these disturbances, Foxp2 mutation contributes to deficits in synaptic plasticity and wiring, whereas corticostriatal circuity results particularly affected. Long term depression at the corticostriatal synapse is impaired (Groszer et al., 2008), and striatum shows aberrant activity modulation during an acquisition task (French et al., 2012). Interestingly, evidence of Foxp2 as modulator of corticostriatal function comes from recordings in anesthetized birds showing that Foxp2 knockdown interferes with dopamine D1R-dependent modulation of activity propagation in a corticostriatal pathway, suggesting that these deficits may be partly attributable to reduced dopamine D1-like receptor and DARPP-32 protein levels (Murugan et al., 2013). Additionally, other study has observed that reduced Foxp2 expression disrupts the excitatory/inhibitory balance in D1-MSNs resulting in motor skill learning deficit. Specifically, Foxp2 reductions lead to a decrease in AMPA/NMDA currents while GABA content at the presynapse of D1-MSNs is increased (Rhijn et al., 2018). Similar findings were found in the medium spiny neurons of the songbird basal ganglia nucleus Area X (Adam et al., 2016).

Several studies have shown the role of Foxp2 as a positive regulator of spine density in several brain regions and species. Knockdown of Foxp2 has been reported to alter spine density and arborization three in the area X of zebra finches (Kosubek-Langer & Scharff, 2020; Schulz et al., 2010). Striatum spine density in Foxp2 KO mice has been also disrupted along with reduction of synaptic markers (Chen et al., 2016). Also, Foxp2 mutation has been reported to decrease dendrite length of layer-VI excitatory neurons in the cortex, while spine density is spared (Druart et al., 2020). Conversely, two studies describe that introducing a partially humanized version of Foxp2 into mice results in a general improvement of synaptic plasticity shown by an increase of the dendrite length, spine density and synaptic markers (Chen et al., 2016; Enard et al., 2009).

Regarding neuronal migration, Foxp2 also seems to play a relevant role supported by the evidence from *in vitro* studies showing the effect of the gene on cell migration phenotypes (Devanna et al., 2014) and differentiation of MSNs (Chiu et al., 2014). From *in vivo* studies it has been documented that disruption of Foxp2 expression during embryonic development induces changes in cortical neurogenesis (Tsui et al., 2013) and in migration of neural progenitors out of the subventricular zone (Garcia-Calero et al., 2016). However, selective deletion of the gene does not recapitulate any of these effects (Kast et al., 2019).

Consistently with the structural abnormalities found in the affected KE family members (Vargha-Khadem et al., 1998), Foxp2 KO mice show severe alterations in brain volume as a dramatic reduction in cerebellar growth, and similarly reductions in the ventral posterior nucleus and the parafasicular nucleus of thalamus (Ebisu et al., 2017; Groszer et al., 2008) corroborating a crucial role in neurodevelopment.

In sum, genetic manipulations of Foxp2 have demonstrated its role in synaptic plasticity and circuit formation. Foxp2 has been proved to be critical for the corticostriatal synapse and the basal ganglia circuit. Moreover, some of the motor impairments observed in Foxp2 deficient mice resemble to those observed in HD mouse models (Hachigian et al., 2017; Shu et al., 2005; Vargha-Khadem et al., 1995). Despite all this knowledge, Foxp2 role in HD has been not fully deciphered, and suggest by its functions could be a keystone in the understanding of neuronal dysfunction in HD.

AIMS

Complex and pathological molecular processes triggered by mHtt along with compensatory mechanisms underlie basal ganglia and synaptic dysfunction in HD. Since transcriptional dysregulation, a key pathogenic mechanism, occurs early in the disease, we hypothesize that transcriptional dysregulation of Foxp2 might also happens at early stages of the disease and in others Foxp2-enriched brain regions, contributing to premature basal ganglia circuitry dysfunction and associated synaptic alterations.

Thus, in this thesis we aimed to elucidate to what extent Foxp2 dysregulation could be a central mechanism in the pathogenesis of HD, and to investigate its potential therapeutic value. To address these questions, we propose the following objectives:

1. To investigate the potential psychiatric-like disturbances in the juvenile R6/1 mouse model and to analyze to what extent Foxp2 regulates these features.
2. To analyze the contribution of Foxp2 to the thalamus-striatal circuit dysfunction and neuropathology, and the associated HD sensory-motor phenotype.

METHODS

1. Animals

Transgenic R6/1 mice (Mangiarini et al., 1996) expressing the N-terminal exon-1 fragment of m*Htt* containing 115 CAG repeats, were used as a murine model of HD. Heterozygous R6/1 male mice were originally acquired from Jackson Laboratory (Bar Harbor, ME, USA) and maintained in a B6CBA genetic background from mating transgenic male mice (C57BL/6J x CBA/J) with F1 females. Genotypes were determined by polymerase chain reaction (PCR) from ear biopsy. Microchips were implanted under the mice skin providing information about their birth, location, and genotype. Transgenic R6/1 mice and WT littermates were housed in numerical birth order in a room kept at 19-22ºC and 40-60% humidity under a 12:12 light/dark cycle with access to water and food *ad libitum*. All experiments were conducted exclusively with male mice to avoid estrus hormonal alterations. WT littermates were used as a control group.

Standard animal procedures were approved by the animal experimentation Ethics Committee of the Universitat de Barcelona (274/18) and Generalitat de Catalunya (10/20), in agreement with the Spanish (RD53/2013) and European (2010/63/UE) regulations for the care and use of laboratory animals.

2. Stereotaxic Surgery

2.1. Intrastriatal injection of monosynaptic rabies virus

To target the pre-synaptic inputs received by the striatum we utilized a two-virus system similar to a previous protocol (Tornero et al., 2017) (Figure 18). Both viruses, the helper lentivirus using the pBOB-Syn-hisGFP-TVA-rabiesG plasmid (titres: 20-30 x 10^6 TU/ml) and the monosynaptic modified rabies EnvA-ΔG-mCherry rabies (titres: 2 × 10^{10} GC/ml) were provided by Dr. Malin Parmar from Lund University, Sweden.

Stereotaxic surgery was performed in 4-week-old and 10-week-old R6/1 male mice and WT littermates by isoflurane-induced anesthesia. Mice were anesthetized with 3.5% isoflurane in 100% oxygen in an induction chamber. Then, fixed in the stereotaxic apparatus anesthetic status was maintained with 1,5% isoflurane. Mouse head was shaved and cleaned with ethanol. Then iodine and local anesthesia was applied (lidocaine 2.5% and prilocaine 2.5% EMLA®, AstraZeneca), and a dose of 2 mg/kg of analgesic Metacam® was injected subcutaneously. Mouse skull was exposed, and the right hemisphere of each animal was drilled in order to deliver viral constructs. 1µl of viral vectors was injected targeting dorsal striatum.

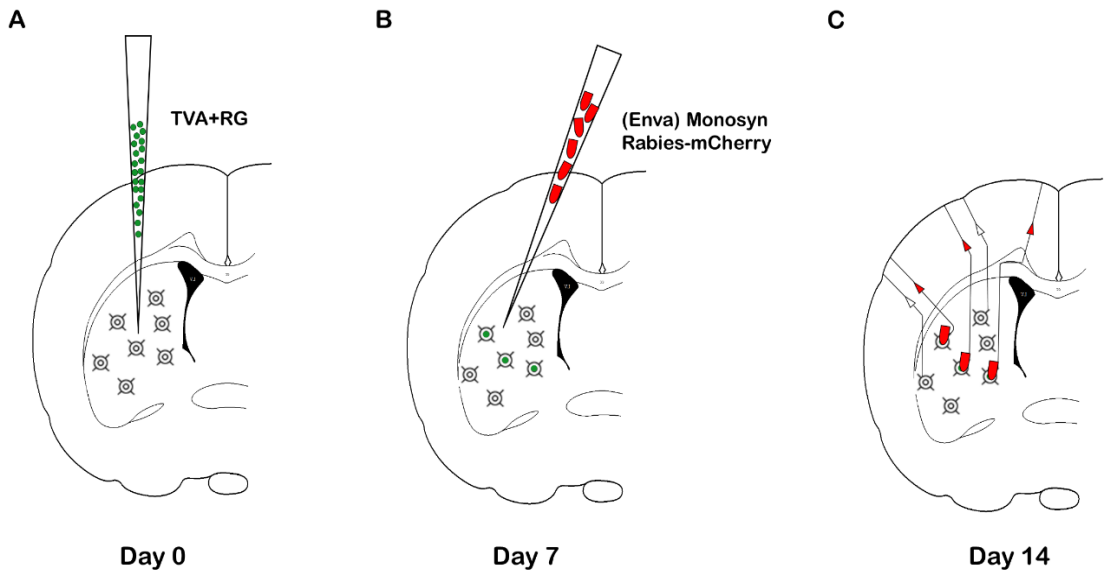


Figure 18. Intrastriatal injection of the helper virus and the monosynaptic rabies virus. (A) First, mouse striatum was injected with the helper lentivirus (TVA+RG). **(B)** One week later the modified rabies virus (Enva) Monosyn Rabies-mCherry was injected at the same coordinate, but along a different injection tract with a 29 degrees tilt to avoid potential double-labeling of cortical cells along the injection tract. **(C)** It took another week for the rabies virus to replicate and spread monosynaptically before tissue processing and analysis.

The following coordinates relative to Bregma (anteroposterior and lateral) and from skull (dorsoventral): AP: -0.5mm; L: +1.8mm and DV: -2.3mm were used for the 4-week-old animals. Meanwhile, for the 10-week-old animals the coordinates were relative to Bregma (anteroposterior and lateral) and from skull (dorsoventral): AP: -0.8mm; L: +2mm and DV: -2.6mm. Viral vectors were injected with a 5µl Hamilton syringe at an infusion rate of 100nl/min. The needle was left in place for 5 min to ensure complete diffusion of the AAVs. Mice were returned to their home cage after fully recovery. After a week, animals were conducted to the second stereotaxic surgery and then infected with the rabies virus. The following coordinates relative to Bregma (anteroposterior and lateral) and from skull (dorsoventral): AP: -0.5mm; L: +3.45mm and DV: -2mm were used for the 4-week-old animals. Meanwhile, for the 10-week-old animals the coordinates were relative to Bregma (anteroposterior and lateral) and from skull (dorsoventral): AP: -0.8mm; L: +3.65mm and DV: -2.35mm. One week later mice were intracardially perfused with 40 mL of PBS, and subsequently with a 40 ml of 4% paraformaldehyde. After perfusion, the brain was isolated and transferred to a post fixative solution containing 4% paraformaldehyde and 30% sucrose in PBS with 0.02% Sodium Azide, and then kept overnight at 4°C. Then, 40µm coronal brain sections were prepared using a vibratome (Leica VT 1000S) and tissue was separated into

four groups to allow for multiple tissue manipulations. Tissue groups that were not used immediately were placed in a cryoprotectant anti-freeze solution (30% glycerol, 30% ethylene glycol and 15% Tris-HCl in H_2Omq) and stored at −20 °C.

2.2 Overexpression of Foxp2

Foxp2-overexpression stereotaxic surgery was conducted in both, transgenic R6/1 mice and WT littermates at different stages and brain regions. At early stages, pups at postnatal day P0-P2 were subjected to bilateral intrastriatal injections. At late stages 12-week-old mice received bilateral intrathalamic injections. Adeno-associated virus (AAV) expressing Foxp2 under CamKII promoter (AAV9-CamKIIa-eGFP-2A-mFoxp2-WPRE) (Vector Biolabs, Pennsylvania, USA) was injected in R6/1 mice (R6/1-Foxp2) and WT mice (WT-Foxp2) and AAV carrying GFP (rAAV5-CamKIIa-eGFP-2A-WPRE) (UNC Vector Cre, North Carolina, USA) used as a control was injected in both R6/1 mice (R6/1-GFP) and WT mice (WT-GFP). Titres of viral construct AAV9-CamKIIa-eGFP-2A-mFoxp2-WPRE were 1.6 x 10^{13} GC/ml. Titres of viral construct rAAV5-CamKIIa-eGFP-2A-WPRE were 5.3 x 10^{12} GC/ml.

2.2.1. Intrastriatal injections of AAV-Foxp2 in R6/1 pups

At postnatal day (P0-P2) R6/1 male mice and WT littermates were subjected to stereotaxic surgery through hypothermia-induced anesthesia. Pups were wrapped in Kleenex tissue and immersed in crushed ice up to the neck for 3 min. Hypothermia-induced anesthetized pups were fixed in the stereotaxic apparatus, their heads were cleaned with ethanol 70%. Skin head and skull were gently penetrated by a sterile needle to performed one incision in each brain hemisphere. 300nl of viral vectors were injected in each incision to bilaterally target the striatum. The following coordinates relative to Lambda (anteroposterior and lateral) and from skull (dorsoventral) were used: AP: +2.4mm; L: +/-1mm and DV: -1.9mm. Viral vectors were injected with a 5µl Hamilton syringe at an infusion rate of 100nl/min. The needle was left in place for 2 min to ensure complete diffusion of the AAVs. After surgery, pups were warm up for 30 min inside a plastic box filled with breeding and heated underneath by an electric blanket. After fully recovery, pups were returned to their home cage.

2.2.2. Intrathalamic injections of AAV-Foxp2 in R6/1 adult mice

Stereotaxic surgery was carried out in 12-week-old R6/1 male mice and WT littermates by isoflurane-induced anesthesia. Mice were anesthetized with 3.5% isoflurane in 100% oxygen in an induction chamber. Then, fixed in the stereotaxic apparatus anesthetic status was maintained with 1,5% isoflurane. Mouse head was shaved and cleaned with ethanol. Then iodine and local anesthesia were applied (lidocaine 2.5% and prilocaine 2.5% EMLA®, AstraZeneca), and a dose of 2 mg/kg of analgesic Metacam® was injected subcutaneously. Mouse skull was exposed and drilled twice to deliver viral constructs. 500nl of viral vectors were injected in each hemisphere targeted bilaterally the thalamus. The following coordinates relative to Bregma (anteroposterior and lateral) and from skull (dorsoventral) were used: AP: -1.7mm; L: +/-1.5mm and DV: -3.5mm. Viral vectors were injected with a 5µl Hamilton syringe at an infusion rate of 100nl/min. The needle was left in place for 5 min to ensure complete diffusion of the AAVs. Mice were returned to their home cage after fully recovery.

2.3. Transduction of AAV-shRNA-Foxp2

Stereotaxical injection of AAVs containing a scrambled shRNA or a shRNA against Foxp2 were used to knockdown Foxp2 expression. Bilateral intrathalamic injections were conducted in 10–11-week-old WT mice, using an AAV produced by Vector Biolabs. AAV expressing shRNAFoxp2 under U6 promoter (AAV8-mCherry-U6-mFoxp2-shRNA) (Vector Biolabs, Pennsylvania, USA) was injected in WT mice (WT-shFoxp2) and AAV carrying mCherry (AAV5-mCherry-U6-scrmb-shRNA) (UNC Vector Cre, North Carolina, USA) used as a control was injected in WT mice (WT-shScr). shRNAs cloning and AAV viral particles production, amplification and purification were done by Vector Biolabs (titres: 8.5 x 10^{12} genomic particles/ml).

2.3.1. Intrathalamic injections of AAV-shRNA-Foxp2 in R6/1 adult mice

Stereotaxic surgery was carried out in 10-12-week-old WT mice by ketamine-xylazine-induced anesthesia. Mice were injected peritoneally with a ketamine-xylazine mixture (100mg/kg; 10mg/kg) dissolved in saline. Animals were then mounted in a rodent stereotaxic apparatus and head-fixed using ear bars, bite bar, and nose clamp. Mouse head was shaved and cleaned with ethanol. Then iodine and local anesthesia was applied (lidocaine 2.5% and prilocaine 2.5% EMLA®, AstraZeneca), and a dose of 2 mg/kg of analgesic Metacam® was injected subcutaneously. Mouse skull was exposed and drilled twice to deliver viral constructs. 500nl of viral vector were injected in each hemisphere targeted bilaterally the thalamus. The following coordinates relative to Bregma (anteroposterior and lateral) and

from skull (dorsoventral) were used: AP: -1.7mm; L: +/-1.5mm and DV: -3.5mm. Viral vectors were injected with a 5µl Hamilton syringe at an infusion rate of 100nl/min. The needle was left in place for 2 min to ensure complete diffusion of the AAVs. Mice were return to their home cage after fully recovery.

3. Behavioral Assessment

3.1. Evaluation of psychiatric disturbances

A behavioral assay designed to evaluate behavioral and psychiatric disturbances was performed in the 3–4-week-old juvenile R6/1 mice and WT littermates (Table 2).

3.1.1. Open Field

A gray open-top square arena (40 cm x 40 cm long; with 30 cm high walls) was placed in a room with dim light (20-25 lux) as described elsewhere (Skillings et al., 2014). Room temperature was kept at 19-22ºC. Mice were placed in the center of the arena and were allowed to explore the arena for 15 min. Animal tracking was recorded via a CCD camera mounted above the arena. Image data acquisition and analysis were performed automatically using Panlab SMART Video Tracking System (3.0). Spontaneous locomotor activity data were inferred by measuring total distance travelled and speed. Spontaneous exploratory activity data were inferred by manually measured number of rearing and grooming events. Time remaining in the center of the arena was determined as a measure of anxiety.

3.1.2. Elevated Plus Maze

The elevated plus maze apparatus consisted of a cross shaped with two opposing situated open arms (30 x 8 cm) against to two other arms (30 x 8 cm) enclosed by 15 cm high walls and a center area. The maze was raised 50cm above the floor and lit with dim light (20-25 lux) as described elsewhere (Pairojana et al., 2021). Mice were placed in the center, facing an open arm, and allowed to explore the maze for 5 min. Animal tracking were recorded via a CCD camera mounted above the maze. Image data acquisition and analysis were performed automatically using Panlab SMART Video Tracking System (3.0). The percentage of the time remaining in the open arms versus time remaining in the closed arms was inferred as a measure of anxiety.

3.1.3. Jumping Test

Jumping behavior was performed as previously described (Matsuoka et al., 2005; Sancho-Balsells et al., 2020). A round platform (an inverted glass container with a diameter of 13 cm and a height of 20 cm) was in a bench of the room. Mice were placed on the platform and allowed to remain for 15 min. The latency to jump out of the platform was registered and was inferred as a measure of impulsivity.

3.1.4. Automated Running Wheels Test

Circadian rhythms were assessed as previously described (Sugiyama et al., 2020). Mice were single housed in cages equipped with in running wheels (ENV-044 Mouse Low-Profile Wireless Running Wheel, Med Associates Inc.; 15,5 cm circumference; 25º from horizontal plane). The cages were placed in a separated room kept at 19-22ºC and 40-60% humidity under a 12:12 light/dark cycle with free access to water and food. Wheel-running activity was monitored through a Wireless transmitter system by using a hub (13.7 x 15.25 cm^2) located in the same room for 3 and/or 4 days. Running wheels revolutions were monitored continuously.

3.1.5. Resident-intruder Paradigm

An adapted resident-intruder paradigm was carried out based on previous protocol (Lutz et al., 2015). After 4 days of single housing resident-intruder test was performed on the day test. Single housed residents were exposed for 10 min to an unfamiliar similar aged intruder (socially housed). Active social behavior as facial and genital sniffing, and active aggressive behavior as physical struggling were manually registered. Animal tracking were recorded via a CCD camera above the arena. Image data acquisition and analysis were performed automatically using Panlab SMART Video Tracking System (3.0).

3.1.6. Forced-swimming test (FST)

Mice were subjected to perform a forced swimming test as described elsewhere (Nakamoto et al., 2020). The apparatus consisted of a transparent plastic cylinder (35 cm height; 20 cm diameter). The cylinder was filled with water (26 ±1 ℃) up to a height of 15 cm. Mice were placed into the cylinder and forced to swim for 6 min. Animal tracking were recorded via a CCD camera mounted in the ceiling room. Image data acquisition and analysis were performed automatically using Panlab SMART Video Tracking System (3.0). Animals escape related mobility behavior was analyzed as a measure of depressive-like behavior.

3.2. Evaluation of sensory-motor function

A behavioral tests battery designed to evaluate motor-sensory deficits was performed in the 16week-old R6/1 mice and WT littermates (Table 2).

3.2.1. Open Field and Novel Whisker-dependent Texture Discrimination Test

Novel whisker-dependent texture discrimination test was conducted as previously reported (Wu et al., 2013) consisted of two consecutive days of habituation in the open field, and one day for testing divided in two sessions: training and testing session (Figure 19). A gray open-top square arena (40 cm x 40 cm long; with 30 cm high walls) was placed in a room with dim light (20-25 lux). The base of the arena was carpeted with 2 cm of standard laboratory bedding. Room temperature was kept at 19-22ºC. Mice were placed in the center of the arena and were allowed to explore the arena for two consecutive day (10 min/per day). Spontaneous locomotor activity data was inferred by measuring total distance travelled and mean speed. Spontaneous exploratory activity data was inferred by manually measured number of rearing events. Time remaining in the center of the arena was determined as a measure of anxiety. On testing day, for the first session mice were placed in the testing arena equidistant to and facing away from two identically smooth-textured objects at the center of the arena. The textured objects were placed in the center of the arena, equidistant to each other and the walls. Mice were allowed to explore the objects for 5 min and then removed and held in a cage for 5 min. Before the second session, the two objects in the arena was replaced with a third, one identically textured object and a novel object with a different texture. The position of the novel rough-textured object versus the familiar smooth-textured object was counterbalanced. Mice were then placed back into the arena for the second session, the test phase, and allowed to explore for 3 min, but only the first minute of exploration of the objects was used for the analysis. The amount of time mice spent actively investigating the objects was recorded. Investigation was defined as directing the nose towards the object (with less than 2 cm from the nose to the object) or touching the object with the nose. Animal tracking were recorded via a CCD camera mounted above the arena. Image data acquisition and analysis were performed automatically using Panlab SMART Video Tracking System (3.0).

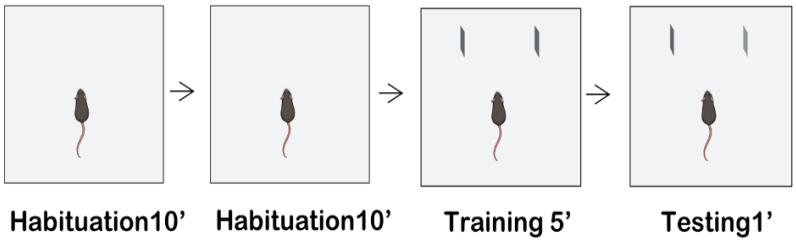


Figure 19. Novel Whisker Texture Discrimination Task (NWDT). The novel whisker texture discrimination paradigm is a dependent task on mystacial vibrissae, performed within 3 days. No appetitive or aversive training is required.

3.2.2. Spontaneous Place Preference Test (SPPT)

Spontaneous place preference test was adapted from (Manita et al., 2015). A gray open-top square arena (40 cm x 40 cm long; with 30 cm high walls) was placed in a room with dim light (20-25 lux). Half of the base of the arena was covered with sandpaper, and the other half was covered with the reverse, smooth side of the sandpaper. The side (left versus right) with the sandpaper was counterbalanced across mice. Mice were placed individually in the arena and were allowed to explore for 10 min. The percentage of preference texture was measured. Animal tracking were recorded via a CCD camera mounted above the arena. Image data acquisition and analysis were performed automatically using Panlab SMART Video Tracking System (3.0).

3.2.3. Accelerating Rotarod

The accelerating rotarod training procedure (ARTP) was conducted as previously described (Fernández-García et al., 2020). To evaluate mouse motor learning and performance, mice were tested on the accelerating rotarod over 2 days. Animals were placed on a horizontal rotating rod (30 mm diameter) with an increasing gradually speed (4 to 40 RPM) over 5 min. Latency to fall was recorded as the time mice spent in the rod before falling. The testing session consisted of 3 trials a day for 2 consecutive days, with a 1h inter-trial interval.

3.2.4. Vertical Pole

Vertical pole test was performed as previously described elsewhere (Creus-Muncunill et al., 2019) to assess mice coordination in the turnover behavior. Vertical pole consisted of a wooden pole wrapped in tape to facilitate walking and held horizontally above porexpan and bedding. Mice were placed just below the top of a vertical pole facing upwards and trained to turn and climb down the pole. Training sessions consisted of 3 trials a day over 2

consecutive days and testing was performed on the third day. Time to complete a turn and the time to climb down the pole were measured.

Table 2. Behavioral Testing. For each test, information about the dimension, the age of animals during the test, and a reference is provided.

BEHAVIORAL TEST	AGE	DIMENSION	REFERENCE
Open Field	3-4week-old 14-15-week-old 16-week-old	Locomotor and exploratory activity	(Skillings et al., 2014)
Elevated Plus Maze	3-4week-old	Anxiety-like behavior	(Pairojana et al., 2021)
Jumping Cliff Avoidance Test	3-4week-old	Impulsive-like behavior	(Matsuoka et al., 2005; Sancho-Balsells et al., 2020)
Automated Running Wheels Test	3-4week-old	Circadian Rhythms	(Sugiyama et al., 2020)
Resident-intruder paradigm	3-4week-old	Social Interaction Aggressive-like behavior	(Lutz et al., 2015)
Forced Swimming Test (FST)	3-4week-old	Depressive-like behavior	(Nakamoto et al., 2020)
Novel whisker-dependent texture discrimination test	14-15-week-old 16-week-old	Whisker-sensory discrimination	(Wu et al., 2013)
Spontaneous place preference test (SPPT)	14-15-week-old 16-week-old	Tactile sensory perception	(Manita et al., 2015)
Accelerating Rotarod	14-15-week-old 16-week-old	Motor learning and coordination	(Fernández-García et al., 2020)
Vertical Pole	16-week-old	Motor coordination in turnover behavior	(Creus-Muncunill et al., 2019)

4. Protein extraction

Mice were killed by cervical dislocation. The brain was quickly removed, and different brain regions (prefrontal and motor cortex, thalamus, hippocampus, and striatum) were quickly dissected out in ice-cold conditions. Frozen brain tissues were homogenized by sonication in ice-cold lysis buffer containing: 1% Triton X-100, 10% Glycerol, 50 mM Tris-HCl pH7.5,

10 mM EDTA, 150 mM NaCl, supplemented with proteases and phosphatase inhibitors: 2mM PMSF (from phenylmethylsulphonyl fluoride), 10 µg/ml Aprotinin,1 µg/ml Leupeptin, 2mM Na3VO4 and 100 mM NaF and protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA). Samples were centrifuged at 16,000 g during 30 min at 4ºC, and supernatant fractions were collected.

Lysates of 4-week-old mice striatum from Foxp2 overexpression experiment were processed for mass spectrometry (MaxQuant run, Proteomic facility, Max Planck Institute of Biochemistry, Martinsried, Germany).

5. Western Blot

Quantification of protein fraction was performed using the Detergent-Compatible Protein Assay (Bio-Rad, Hercules, CA, USA). Protein extracts (normally 20 µg) were denatured in 62.5 mM Tris-HCl (pH 6.8), 2% Sodium dodecyl sulfate (SDS), 10% glycerol, 140 mM b-mercaptoethanol and 0.1% bromophenol blue and heated at 100ºC for 5 min. Protein extracts were resolved in denaturing SDS–polyacrylamide gel electrophoresis (SDS-PAGE), with variable polyacrylamide concentration depending on the molecular weight of the protein of interest, at 35 mA/gel over 1 h. The Precision Plus Protein™ Dual Color ladder (Bio-Rad) was loaded along with the protein samples to properly identify the protein of interest. Afterwards, proteins were transferred to a nitrocellulose membrane (Whatman Schleicher & Schuell, Keene, NH, USA) during 1.5 h at 90 V at 4ºC. Membranes were stained momentarily using Ponceau S reagent to validate protein transfer and rinsed with Tris-buffered saline, 0.1% Tween 20 (TBS-T) to remove staining. Non-specific protein binding sites were blocked during 1 h incubation in blocking solution containing 10% non-fat powdered milk in TBS-T (50 mM Tris-HCl, 150 mM NaCl, pH 7.4, 0.05% Tween 20). Membranes were rinsed 3 times during 10 min in TBS-T and immunoblotted overnight at 4°C with the primary antibody (Table 3).

Table 3. Primary antibodies used for Western blot.

ANTIGEN	REFERENCE	MW (kDa)	HOST SPECIE	DILUTION	SOURCE
Actin	69100	42	Mouse	1:20,000	MP Biochemicals (Aurora, OH, USA)
GABA-A α1	224 211	50	Mouse	1:1000	Synaptic Systems (Göttingen, Germany)

GABA-A α2	224 104	50	Guinea Pig	1:1000	Synaptic Systems (Göttingen, Germany)
GABRβ3	SAB200049	55	Mouse	1:1000	Sigma-Aldrich (St. Louis, MO, USA)
Foxp2	ab16046	75	Rabbit	1:1000	Abcam (Cambridge, UK)
Phospho-PKAcat	Sc-903	42	Rabbit	1:1000	Santa Cruz Biotechnology (Santa Cruz, CA, USA)
Phospho-PKA substrate	9624S	SMEAR	Rabbit	1:1000	Cell Signaling Technology (Beverly, MA, USA)
Tyrosine Hydroxylase	NB 300-100	60	Sheep	1:1000	Novus Biologicals (Littleton, CO, USA)
α-Tubulin	T-9026	55	Mouse	1:50,000	Sigma-Aldrich (St. Louis, MO, USA)

Membranes were then rinsed 3 times for 10 min each with TBS-T and incubated with the proper horseradish peroxidase-conjugated secondary antibody for 1 h at room temperature (Table 4).

Table 4. Secondary antibodies used for Western blot. All secondary antibodies were conjugated with the horseradish peroxidase.

ANTIGEN	REFERENCE	DILUTION	SOURCE
Anti-mouse IgG	SA1-100	1:2000	Promega (Madison, WI, USA)
Anti-rabbit IgG	SA1-200	1:2000	Promega (Madison, WI, USA)
Anti-guinea-pig IgG	ab97155	1:2000	Abcam (Cambridge, UK)
Anti-sheep IgG	ab97130	1:2000	Abcam (Cambridge, UK)

Membranes were washed thrice for 10 min each with TBS-T and were developed using luminol reagent (Santa Cruz Biotechnology, Santa Cruz, CA, USA) in the Chemidoc MP Imaging System (Bio-Rad, California, USA). Gel-Pro densitometry program (Gel-Pro 3.2

Analyzer for Windows-version) was used to quantify the intensity of the different immunoreactive bands relative to the intensity of the loading controls. As loading control were used α-Tubulin or actin.

6. Immunofluorescence

Brain hemispheres used for immunohistochemistry were post-fixed with paraformaldehyde 4% (PFA), and then kept in PBS with 0.02% Sodium Azide at 4ºC until use. Coronal sections (40 μm) of the brain were obtained using a vibratome (Leica VT 1000S) or a microtome (Leica SM 2000R) and kept in cryoprotectant anti-freeze solution at -20ºC until use.

Free-floating brain sections were rinsed twice in PBS for min and incubated 2 times for 15 min each with 50 mM NH_4Cl to reduce aldehyde-induced tissue autofluorescence. Sections were permeabilized twice for 10 min each with PBS containing 0.5% Triton X-100. Thereafter sections were blocked with PBS containing 0.3% Triton X-100, 0.2% sodium Azide and 5% normal donkey serum/goat serum (Pierce Biotechnology, Rockford, IL) for 2 h at room temperature. Then, sections were incubated overnight at 4ºC with primary antibody diluted in a solution of PBS containing 0.3% Triton X-100, 0.2% Sodium Azide and 5% normal donkey serum/goat serum (Table 5).

Table 5. Primary antibodies used for Immunofluorescence.

ANTIGEN	REFERENCE	HOST SPECIE	DILUTION	SOURCE
GFP FITC	ab6662	Goat	1:500	Abcam (Cambridge, UK)
EM48	MAB5374	Mouse	1:150	Millipore (Burlington, MA, USA)
DARPP-32	611520	Mouse	1:1000	BD Transductions (San José, CA, USA)
Foxp2	ab16046	Rabbit	1:100	Abcam (Cambridge, UK)
PSD95	3450	Rabbit	1:300	Cell Signaling Technology (Beverly, MA, USA)
RFP	600-401-379	Rabbit	1:500	Rockland (Pottstown, PA, USA)

VGluT2	AB2251-I	Guinea pig	1:1000	Millipore (Burlington, MA, USA)

The next day, the sections were washed thrice with PBS for 10 min and then incubated 1.5h at room temperature with secondary antibodies diluted in PBS (Table 6).

Table 6. Secondary antibodies used for Immunofluorescence.

ANTIGEN	REFERENCE	DILUTION	SOURCE
Goat anti-rabbit Cy3 555	111-165-144	1:200	Jackson ImmunoResearch (West Grove, PA, USA)
Goat anti-mouse Cy3 555	115-165-003	1:200	Jackson ImmunoResearch (West Grove, PA, USA)
Goat anti-guinea pig Alexa Fluor 647	106-605-003	1:200	Jackson ImmunoResearch (West Grove, PA, USA)
Donkey anti-mouse Cy3 555	715-165-150	1:200	Jackson ImmunoResearch (West Grove, PA, USA)
Donkey anti-mouse Alexa Fluor 488	715-545-150	1:200	Jackson ImmunoResearch (West Grove, PA, USA)

Hereafter, slices were covered with foil and protected from the light to avoid fluorescence photobleaching. After washing thrice from 10 min each with PBS, nuclei were stained with DAPI (Sigma-Aldrich) for 15 min. After three more washes of 10 min each in PBS slices were mounted in the slides and left until dry completely. Lastly, slides were covered in the mounting media and the coverslips.

7. Golgi Staining

Fresh brain hemispheres were processed following the Golgi-Cox method as described elsewhere (Giralt et al., 2017). Mouse brain hemispheres were incubated in the dark for 21 days in filtered dye solution consisted of 1% potassium dichromate, 1% mercury chloride and 0.8% potassium chromate. Consecutively brain tissue was washed 3 times for 2 min each in distilled water and 30 min in 90% ethanol. Thereafter, brain hemispheres were cut in 200μm sections in 70% ethanol on a vibratome (Leica VT 1000S) and washed in distilled water for 5 min. The 200μm sections were then reduced in 16% ammonia solution for 1 h, washed in water for 2 min and fixed in 1% sodium thiosulfate for 7 min. After reduction and

a 2 min final wash in water, sections were mounted on super frost coverslips and dehydrated for 3 min in 50, 70, 80 and 100% ethanol, incubated twice for 5 min each in a 2:1 isopropanol/ethanol mixture, followed by 5 min incubation in pure isopropanol and twice incubation of 5 min each in xylol. Finally, samples were mounted with mounting medium (DPX, Merck) and let them dry. Secondary dendrites from striatum or cortex were photographed, with a maximum of two-three dendrites per neuron and from at least 3 slices per animal. Z-stacks from 0.2µm sections were obtained in bright field at x63 resolution on a Widefield AF6000 Monochroma Camera Leica Microscope.

8. Dendritic Spine Analysis

Images were analyzed with the ImageJ software. Secondary dendritic segments (>20 µm long) were selected and traced. The total number of spines was obtained using the cell counter tool from ImageJ. Dendritic spine density was obtained after dividing the number of spines by the length of the segment (nº spines/µm).

9. Nissl staining

Nissl staining protocol was performed as previously reported elsewhere (Giralt et al., 2011). Mice brain sections were mounted in coating slides and let them dry for 2 h. Sections were then stained in 0.1% cresyl violet (Nissl stain) for 45 min, dehydrated for 1 min in 70, 90 and 100% ethanol and incubated twice in Xylol for 5 min each. Finally, slices were mounted with mounting medium (DPX, Merck) and let them dry.

10. Cytochrome C Oxidase

Cytochrome C Oxidase protocol was carried out as previously reported (Engmann et al., 2015). Sections were washed in PB 0.1M, and then incubated for 10 h in 10% sucrose, 0,1 g/l cytochrome C from equine heart (Sigma) and 0.125 g/l DAB (Sigma-Aldrich) at 37ºC. Henceforth, brain sections were washed in PB 0.1M, mounted then in coating-gelatin slides and let dry for 24 h. Next day, sections were dehydrated for 3 min in 70, 80, 90 and 100% ethanol and incubated in Xylol for 1 h. Slices were finally mounted with mounting medium (DPX, Merck) and let them dry.

11. Unbiased stereology

Striatal and thalamic volumes of Nissl-stained brain sections were estimated using the Cavalieri method as previously described (Giralt et al., 2010).

12. Estimation of monosynaptic tracer cells

Slides were scanned with an Olympus BX51 microscope (Olympus, Ballerup, Denmark). Sections were analyzed using the Optical Fractionator technique and the VIS software package (version 7.0.3.3313). Cortical and thalamic neuronal inputs to striatum were obtained by counting tracer cells (marked in red) that fell within a 10 cm × 10 cm grid size at 40× and within 40 μm of the thickness of the section. Striatal starter cells were obtained by counting cells (marked in green and red) that fell within a 10 cm × 10 cm grid size at 40× and within 40 μm of the thickness of the section. For each animal, the number of cortical and thalamic tracer neurons was divided by the number of striatal starter cell to normalize the proportion of the afferent inputs according to the widespread of striatal transduced neurons.

13. Quantification of cortical somatosensory thickness

Thickness quantification of the somatosensory cortex were performed similar to previous protocol (Fenlon et al., 2015) selecting at least 9 consecutive and comparable brain sections from each mouse.

14. Statistical Analysis

Statistical analysis was performed using Student's two-tailed t-test and two-way ANOVA. Tukey's Honestly Significant Difference test (HSD), Bonferroni's and Sidak's multiple comparisons post hoc tests were conducted as indicated in the figure legends. Data analysis and graphs were created using GraphPad Prism Software (Version 8.0). A 95% confidence interval was used and values with a $p < 0.05$ were considered statistically significant. Data was expressed as mean ± SEM.

RESULTS

1. Expression and distribution of Foxp2 in the R6/1 mouse model

1.1. Foxp2 protein levels are early decreased in the striatum of juvenile R6/1 mice

To investigate whether the endogenous Foxp2 protein was altered in the R6/1 mouse model, we analyzed Foxp2 protein levels in striatal extracts obtained from R6/1 mice and WT controls. Striatal samples were analyzed along the disease progression and the different symptomatic stages: asymptomatic stage (PND3, PND15, 4 and 8 weeks), early symptomatic stage (12 weeks), and late symptomatic stage (20 weeks). Interestingly, western blot analysis revealed that endogenous Foxp2 expression was significantly altered from PND15 (t_{19}=3.896, p=0.0010) and remained altered at 4 weeks (t_{10}=4.325, P=0.0003), 8 weeks (t_{11}=2.808, p=0.0170), 12 weeks (t_{10}=7.775, p<0.0001) and 20 weeks (t_{12}=6.373, p<0.0001) in the transgenic R6/1 mice striatal tissue compared to the WT mice. Also, two-way ANOVA showed a significant time effect on Foxp2 reductions levels ($F_{(5,74)}$=6.056; p<0.0001) (Figure 20).

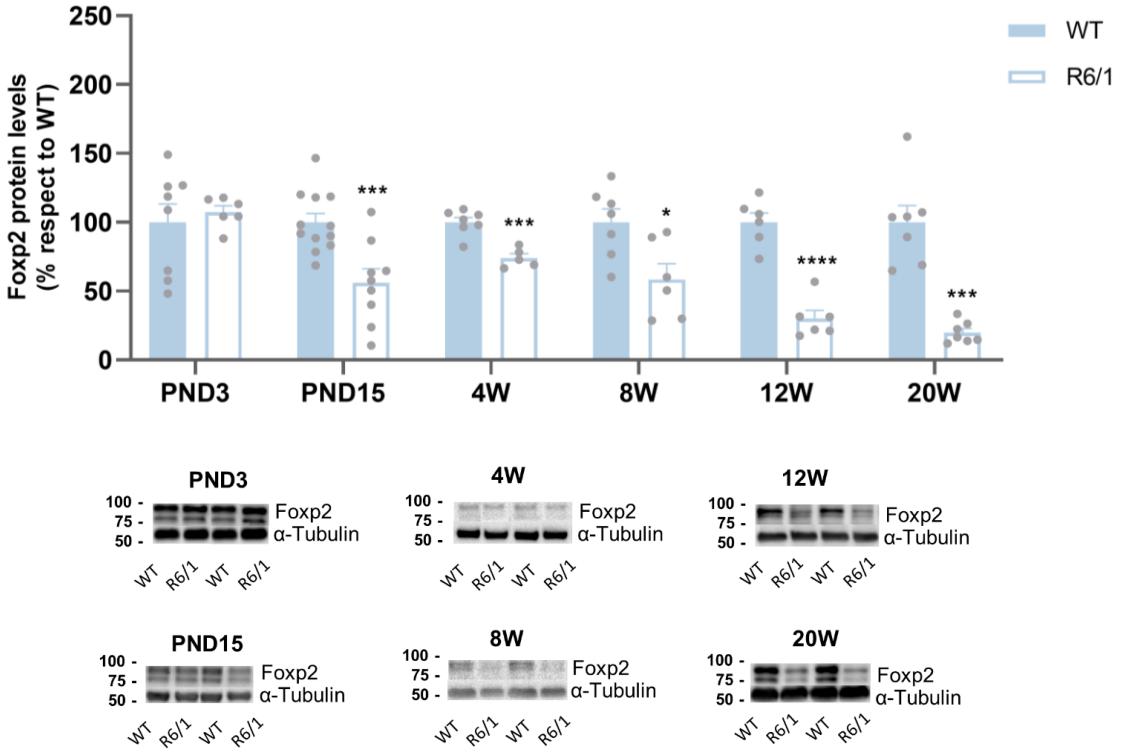


Figure 20. Expression of endogenous Foxp2 in the R6/1 mice striatum. Densitometric analysis showing protein levels of Foxp2 in WT and R6/1 striatum at PND3, PND15, 4, 8, 12 and 20 weeks. Protein levels were normalized with tubulin as loading control. Representative immunoblots are shown below. Data were analyzed

by Student's two-tailed t test. *p < 0.05, ***p < 0.001, ****p < 0.0001 and two-way ANOVA for age factor, with genotype and age as factors. Data were expressed as (mean ± S.E.M) (n=6-11 animals per genotype).

1.2. Foxp2 protein levels are altered in the dorsal striatum of juvenile R6/1 mice, but not in NAcc

To further investigate if the reduction of Foxp2 protein levels was restricted to different subregions or, in contrast, was homogenous in the whole striatum, we next performed an immunofluorescence against Foxp2 to elucidate localization and expression in the juvenile 4-week-old R6/1 mice striatum and age-matched WT controls. Foxp2 intensity was measured in coronal sections of the dorsal striatum and NAcc (Figure 21A). Interestingly, we found a significant reduction of Foxp2 protein levels in the dorsal striatum of juvenile R6/1 mice compared to WT littermates (t_8=2.654, p=0.0291) (Figure 21B, C), however in NAcc region the expression of Foxp2 protein was unchanged (t_7=0.9226, p=0.3869) (Figure 21D).

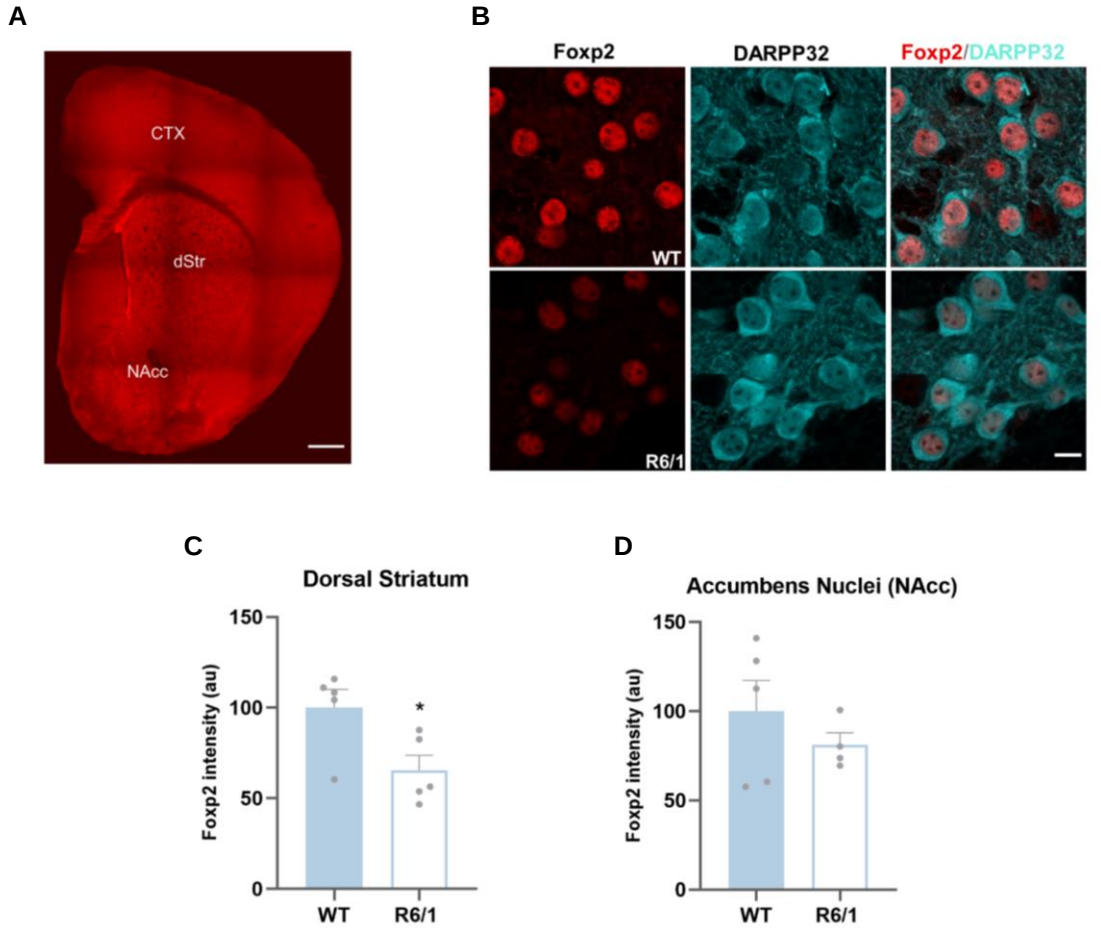


Figure 21. Expression and distribution of endogenous Foxp2 in the dorsal striatum and NAcc of juvenile R6/1 mice (A) Photomicrograph showing Foxp2 expression in a WT brain mouse. Scale bar: 500µm. **(B)** Representative photomicrographs (high magnification) showing Foxp2 nuclei expression and localization

in the striatum of R6/1 mice and WT controls. Scale bar: 10µm. **(C)** Histogram shows quantification of the average of Foxp2-positive nuclei in the striatum. **(D)** Histogram shows quantification of the average of Foxp2-positive nuclei in the NAcc. Data were analyzed by Student's two-tailed t test. *p < 0.05. Data were expressed as (mean ± S.E.M) (n=4-5 animal per genotype).

1.3. Foxp2 protein levels are also decreased in the cortex of the adult R6/1 mice

To evaluate to what extent endogenous Foxp2 levels could be changed in our mouse model, we next tested Foxp2 protein levels in the R6/1 mice cortex and WT controls. Cortical samples representing all the symptomatic stages of the disease were analyzed by Western blot: asymptomatic stage (PND3, PND15, 4 and 8 weeks), early symptomatic stage (12 weeks), and late symptomatic stage (20 weeks). Interestingly, western blot analysis revealed that endogenous Foxp2 expression was affected at 8 weeks (t_{11}=7.437, p<0.0001), 12 weeks (t_{12}=6.143, p<0.0001) and 20 weeks (t_{10}=10.70, p<0.0001). However, at younger ages as PND3 (t_{10}=0.4194, p=0.6840), PND15 (t_{11}=0.7020, p=0.4973) or 4 weeks (t_{12}=0.9250, p=0.3732), Foxp2 expression was similar in the R6/1 mice cortex compared to WT. Also, a two-way ANOVA showed a significant time effect on Foxp2 reductions levels ($F_{(5,66)}$=5.271; p=0.0004) (Figure 22).

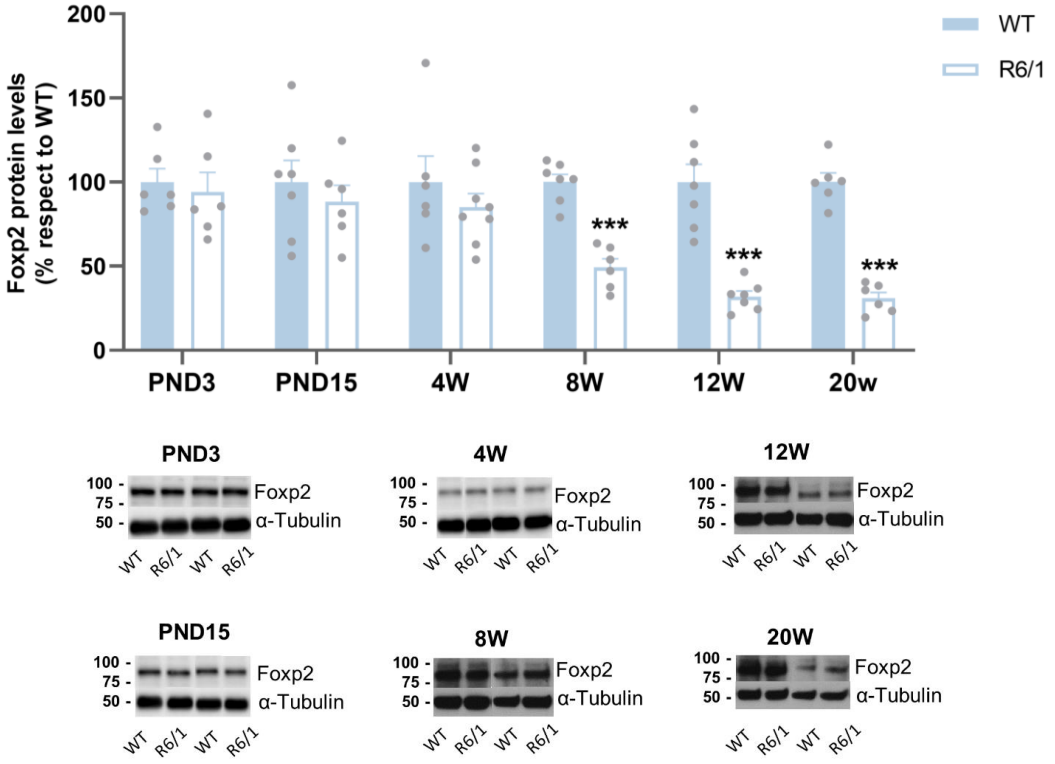


Figure 22. Expression of Foxp2 in the R6/1 mice cortex. Densitometric analysis showing protein levels of Foxp2 in WT and R6/1 mice cortex at PND3, PND15, 4, 8, 12 and 20 weeks. Protein levels were normalized with tubulin as loading control. Representative immunoblots are shown below. Data were analyzed by Student's

two-tailed t test. ***p < 0.001 and two-way ANOVA for age factor, with genotype and age as factors. Data were expressed as (mean ± S.E.M) (n= 6-8 animals per genotype).

1.4. Foxp2 partially colocalizes with mHtt in juvenile R6/1 mice striatum

Intracellular aggregates are the most distinctive histopathological feature of HD. These aggregates are mainly formed in the nucleus by N-terminal fragments of huntingtin, but they are also present in the cytoplasm (Davies et al., 1997). EM48 antibody raised against the N-terminal region (amino acids 1-256) of human huntingtin has proved to selectively recognize aggregates forms in rodents (Dragatsis et al., 2009). Using this staining, previous studies have demonstrated that R6/1 mouse brain shows a nuclear EM48 labeling with a greater density of nuclear and neuropil aggregates (Gutekunst et al., 1999). Even when is not described that those intracellular aggregates occur at so young stages as Foxp2 reduced expression, we found necessary to rule out the possibility of a mHtt-dependent sequestration of Foxp2 inside the intracellular inclusions as an explanation of the reduced levels of Foxp2. Therefore, to elucidate if endogenous Foxp2 in 4-week-old R6/1 mouse striatum was potentially decreased due to the presence of aggregates, we performed a double immunofluorescence against Foxp2 and EM48 in coronal striatal sections. Unexpectedly, we found nuclear diffuse staining and spheric and distinctly round immunolabeled nuclear inclusions in the striatum of juvenile R6/1 mouse. Also, Foxp2 staining showed a partial co-aggregation with mHtt (Figure 23).

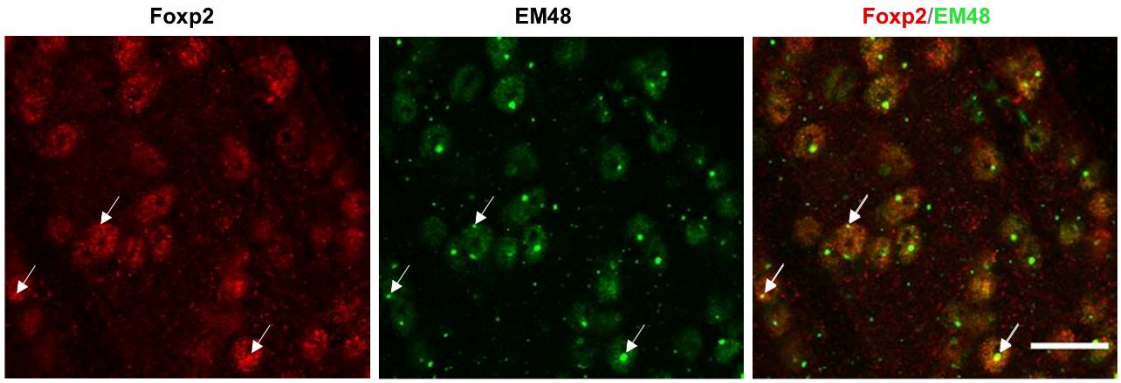


Figure 23. Foxp2 colocalization with mHtt in the juvenile R6/1 mice striatum. Representative photomicrographs (high magnification) showing colocalization of Foxp2 nuclei expression and EM48 (arrows) labelling in the striatum of R6/1 mice and WT controls. Scale bar: 20μm.

2. Behavioral assessment of psychiatric-like disturbances in juvenile R6/1 mice model

2.1. Juvenile R6/1 mice display hyperlocomotive behavior

Foxp2 alterations underlie several psychiatric-like behavioral deficits (Khanzada et al., 2017) including impulsivity, hyperactivity, and social disturbances (Medvedeva et al., 2019; Ribasés et al., 2012). Since juvenile R6/1 mice showed early diminished Foxp2 proteins levels, we next subjected juvenile R6/1 mice and age-matched WT controls to a set of behavioral tests (Figure 24A). We measured locomotor and exploratory activity in 15 min open-field test and found that juvenile R6/1 mice traveled for longer distances (t_{28}=4.093, p=0.0003) (Figure 24B), at higher speed ratio (t_{26}=2.423, p=0.0227) (Figure 24C), and for longer times at fast speed (t_{26}=2.281, p=0.0310) than WT mice (Figure 24D). These results indicate the presence of hyperlocomotive behavior in the 3–4-week-old R6/1 juvenile mouse. We did not observed differences between genotypes in time in the center of the arena (t_{26}=1.518, p=0.1411), suggesting similar levels of anxiety-like behavior in both groups (Figure 24E). Parallel index (higher values means straighter walking), an altered parameter in some neurological conditions (Negishi et al., 2012), was similar between genotypes (t_{26}=0.9956, p=0.3286), suggesting no alterations in the directionality of the free walking of mice (Figure 24F).

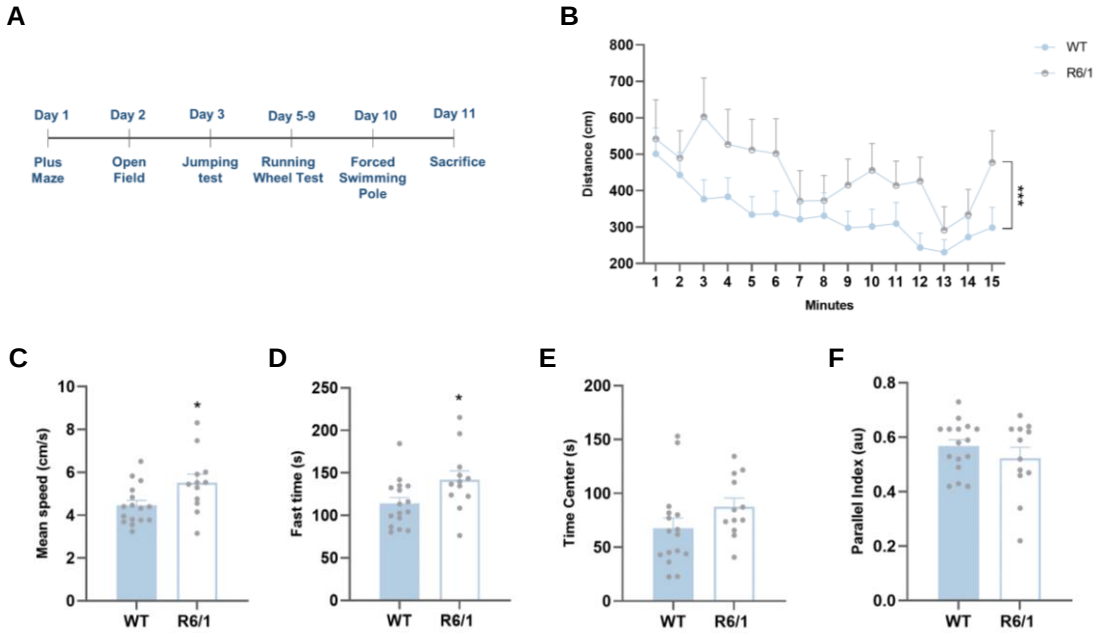


Figure 24. Assessment of the locomotor activity in the juvenile R6/1 mice. (A) Timeline of behavioral testing in juvenile R6/1 mice and WT controls. **(B)** Distance in the open field. **(C)** Mean speed. **(D)** Fast time. **(E)** Time in the center of the arena. **(F)** Parallel index. Data were analyzed by Student's two-tailed t test. *p < 0.05 and ***p < 0.001. Data were expressed as (mean ± S.E.M) (n=12-16 animals per genotype).

2.2. Juvenile R6/1 mice and WT littermates do not show anxiety- and depressive-like behaviors

Within the battery of behavioral tests (Figure 24A), we tested the presence of anxiety-like behavior in the 3-4-week-old R6/1 mice by performing a plus maze test (Figure 25A). Both, R6/1 mice and WT littermates spent similar percentage of the time in the plus-maze open arms (t_{26}=0.4320, p=0.6693) (Figure 25B) and closed arms (t_{26}=0.2682, p=0.7907) (Figure 25C), suggesting no differences in anxiety-like behavior between genotypes. To test any signs of depressive-like behavior we performed a forced swimming test (Figure 25D), but we did not observe differences in immobility duration either, at the first 2 min (t_{24}=0.2319, p=0.8186) (Figure 25E) or at the last 4 min (t_{26}=0.4739, p=0.4739) (Figure 25F), suggesting similar levels of performance between genotypes.

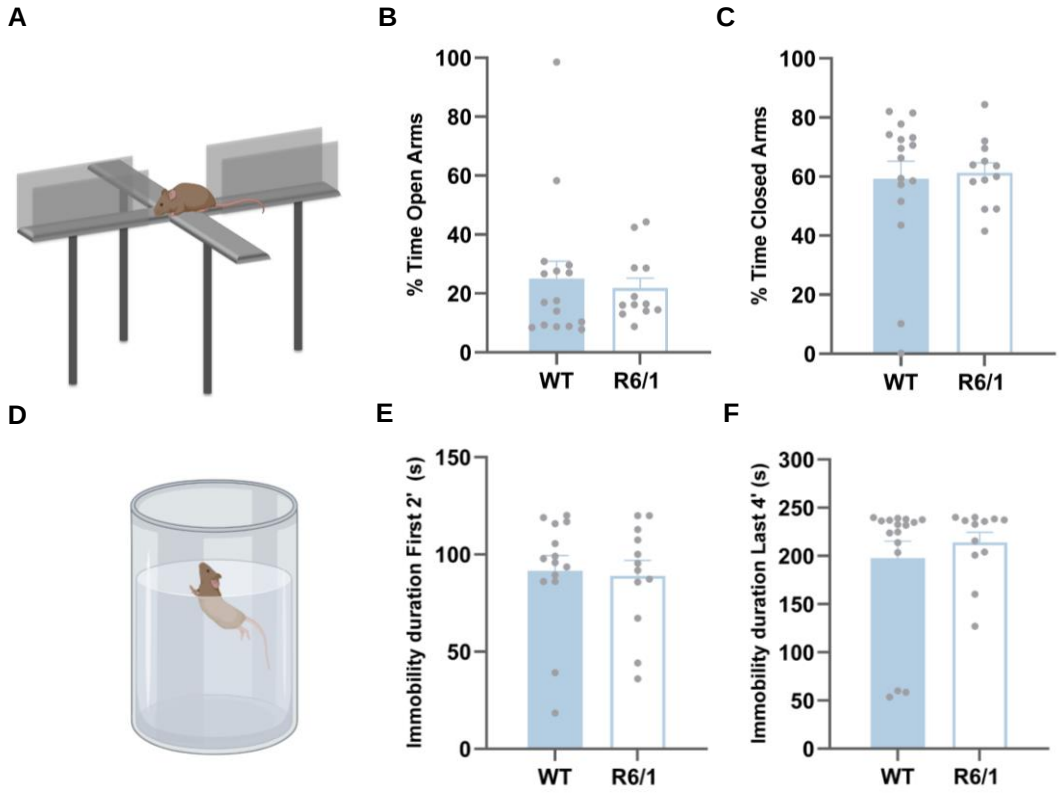


Figure 25. Juvenile R6/1 mice performance in the plus maze and in the forced swimming test. (A) Plus maze test. **(B)** Time spent in the open arms. **(C)** Time spent in the closed arms. **(D)** Forced Swimming pole test. **(E)** Immobility duration in the first 2 min of the forced swimming pole test. **(F)** Immobility duration in the last 4 min of the forced swimming pole test. Data were analyzed by Student's two-tailed t test. Data were expressed as (mean ± S.E.M) (n= 12-16 animals per genotype).

2.3. Juvenile R6/1 mice exhibit impulsive-like behavior

Within the battery of behavioral tests (Figure 24A), we assessed the presence of impulsive-like behavior in the 3-4-week-old R6/1 mice and WT littermates by performing the cliff-avoidance jumping test (Matsuoka et al., 2005) (Figure 26A). Interestingly, we observed that juvenile R6/1 mice manifest a significant increase in impulsive-like behavior by spending less time in the round platform than WT mice (t_{39}=2.718, p=0.0098) (Figure 26B).

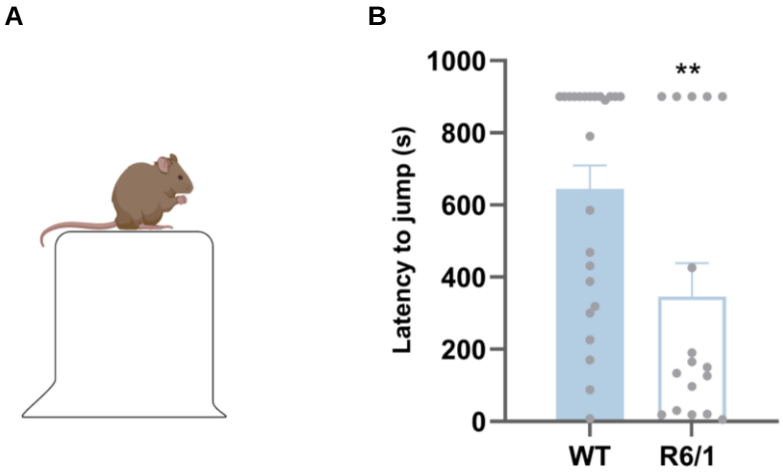


Figure 26. Juvenile R6/1 mice performance in the cliff avoidance test. (A) Cliff avoidance jumping test. **(B)** Latency to jump out of the platform in the cliff avoidance jumping test. Data were analyzed by Student's two-tailed t test. **p < 0.01. Data were expressed as (mean ± S.E.M) (n=18-24 animals per genotype).

2.4. Juvenile R6/1 mice show altered locomotor circadian rhythms

Next, we assessed the free-running period of locomotor activity in automated running wheels of 3-4-week-old R6/1 mice and WT controls for 3 days (Figure 27A). We observed differences between groups in general activity cycle. Two-way ANOVA showed a time ($F_{(5,190)}$=71.87; p<0.0001), genotype ($F_{(1,38)}$=6.824; p=0.0128), and interaction effect ($F_{(5,190)}$=2.799; p=0.0183). Bonferroni post hoc analyses showed a significant increase in the activity levels of the juvenile R6/1 mice compared to WT littermates, at 12 hours (p=0.0112) and 60 hours (p=0.0134) of the dark cycle (Figure 27B). During dark cycle or times of high activity R6/1 mice showed longer free-running period, suggesting a disruption of locomotor circadian rhythms (Figure 27C). Two-way ANOVA showed a time ($F_{(2,76)}$=4.973; p=0.0093) and genotype effect ($F_{(1,38)}$=5.450; p=0.0250) but did not show an interaction effect ($F_{(2,76)}$=0.1982; p=0.8207). During light cycle or times of low activity juvenile R6/1 mice and WT controls displayed similar levels of activity. Neither time ($F_{(2,74)}$=1.410; p=0.2507), nor genotype ($F_{(1.37)}$=1.778; p=0.1906), nor interaction effect ($F_{(2,74)}$=2.727; p=0.0720) was observed (Figure 27D).

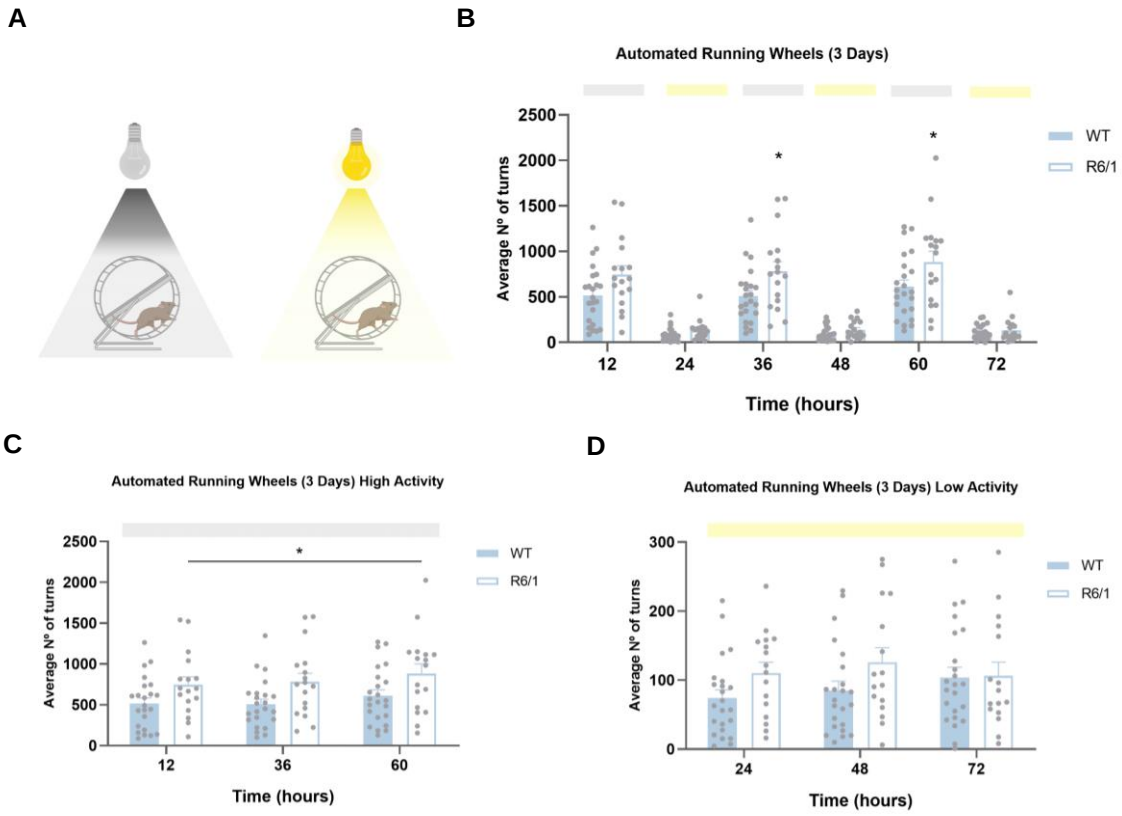


Figure 27. Measurement of free-running period in juvenile R6/1 mice during the light/dark cycle. **(A)** Running Wheels Paradigm during the light/dark cycle. **(B)** Free-running period for 3 days. **(C)** Free-running period during dark cycle. **(D)** Free-running period during light cycle**.** Data were analyzed by repeated measures ANOVA with genotype and time as factors. *$p < 0.05$. Bonferroni's post hoc test was performed. Data were expressed as (mean ± S.E.M) (n= 17-24 animals per genotype).

3. Normalization of Foxp2 levels in the striatum of juvenile R6/1 mice

As mentioned before, Foxp2 alterations underlie several psychiatric-like behavioral deficits (Khanzada et al., 2017). As described previously in the present thesis, some of those psychiatric-like behavioral deficits were found in our juvenile R6/1 mouse model. To investigate whether a therapeutic intervention could restore these alterations, we next injected juvenile R6/1 mice and age-matched WT controls striatum with an AAV9 containing Foxp2 to recover basal levels and subjected the mice to a similar battery of behavioral test than the previous one. R6/1 and WT mice control groups were injected with an AAV5 expressing only GFP (Figure 28).

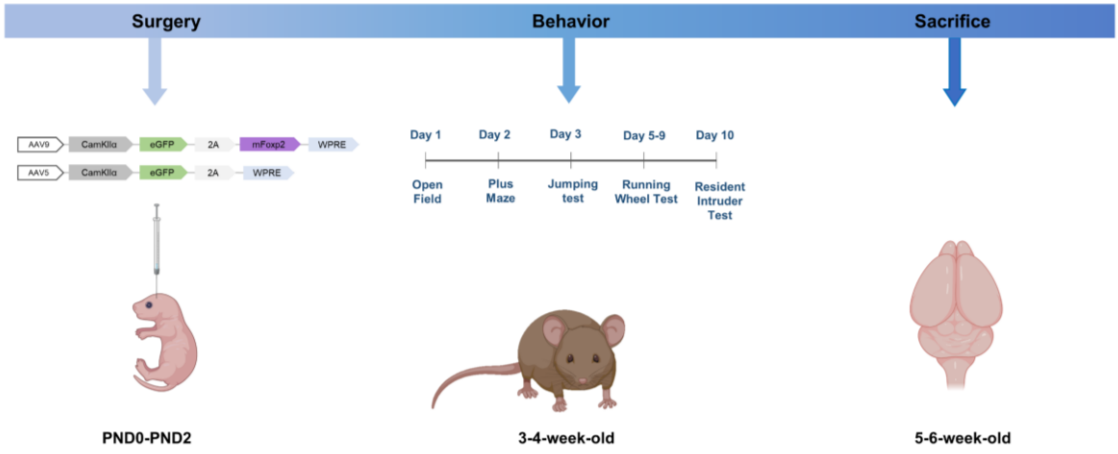


Figure 28. Experimental design of the Foxp2 recovery approach.

3.1. Restoration of the striatal Foxp2 levels in juvenile R6/1 mice

To validate the overexpression of Foxp2 in the juvenile R6/1 and WT mice striatum we performed an immunofluorescence against Foxp2 and GFP signal. A double labelling Foxp2-GFP revealed a widespread viral transduction in the striatum (Figure 29A). Two-way ANOVA analysis showed significant differences between juvenile R6/1 and WT control mice ($F_{(1,38)}$=26.79; p<0.0001), corroborating the Foxp2 downregulation previously observed in transgenic mice. Foxp2 overexpression in the striatum was confirmed by a significant difference in treatment factor ($F_{(1,38)}$=11.19; p=0.0019), although significant interaction effect was not observed ($F_{(1,38)}$=0.3454; p=0.5602). Despite the lack of interaction, Tukey's multiple comparison test showed that Foxp2 intensity in R6/1-Foxp2 was significantly greater than in R6/1-GFP (p=0.0401) (Figure 29B, C).

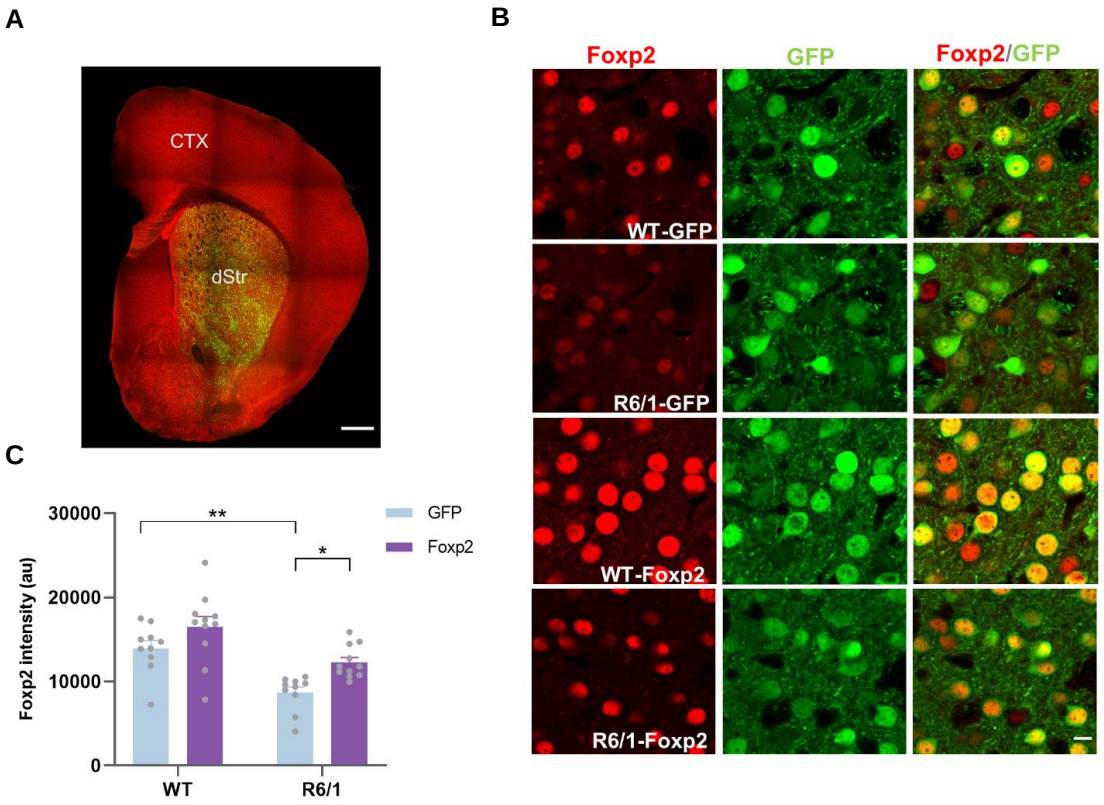


Figure 29. Expression and distribution of Foxp2 in the transduced juvenile R6/1 mice. (A) Representative photomicrograph of AAV9 virus site of injection in the striatum. Scale bar: 500µm. **(B)** Representative photomicrographs (high magnification) showing double labelling of Foxp2 and GFP in the striatum of WT-GFP, R6/1-GFP, WT-Foxp2 and R6/1-Foxp2. Scale bar: 10µm. **(C)** Histogram shows quantification of the average of Foxp2-positive nuclei in the striatum. Data were analyzed by two-way ANOVA with genotype and treatment as factors. Tukey's pos hoc was performed. Data were expressed as (mean ± S.E.M) (n=9-11 mice per group).

3.2. Transduced juvenile R6/1 mice do not recapitulate hyperlocomotive behavior

We tested the four experimental groups WT-GFP, R6/1-GFP, WT-Foxp2 and R6/1-Foxp2 to a battery of behavioral tests (Figure 30A). We first assessed locomotor and exploratory activity in 15 min open-field test and found that the four experimental groups traveled similar distances (Figure 30B), at similar speed ratio (Figure 30C), and for similar times at high speed (Figure 30D). Surprisingly, R6/1-GFP mouse does not recapitulate the hyperlocomotive behavior previously showed. Also, similar to observed in Figures A, B, C, the four experimental groups showed similar time in the center of the arena (Figure 30E), and similar parallel index (Figure 30F). All these data suggest that Foxp2 overexpression had not effects neither in anxiety-like behavior nor walking directionality in none of the groups. Absence of the R6/1 mouse hyperlocomotive phenotype makes it difficult to find out the potential role of Foxp2 in the reversion of hyperlocomotive-like behavior.

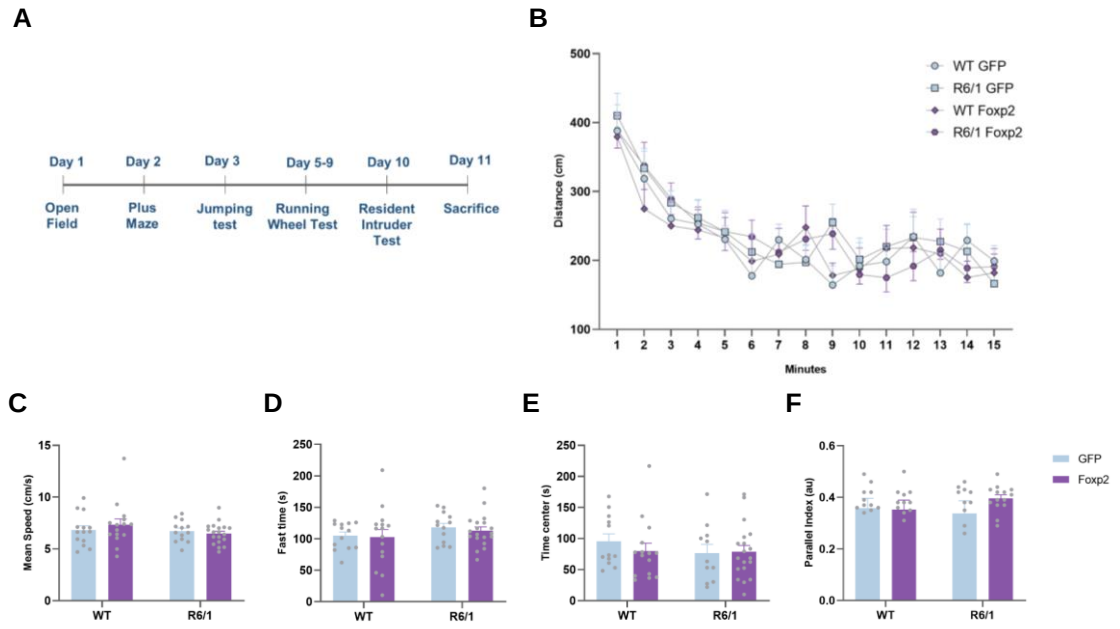


Figure 30. Assessment of the locomotor activity in the transduced juvenile R6/1 mice. (A) Timeline of behavioral testing in WT-GFP, R6/1-GFP, WT-Foxp2 and R6/1-Foxp2. **(B)** Distance in the open field. **(C)** Mean speed. **(D)** Fast time. **(E)** Time in the center of the arena. **(F)** Parallel index. Data were analyzed by a two-way ANOVA with genotype and treatment as factor. Data were expressed as (mean ± S.E.M) (n=14-19 animals per group).

3.3. Foxp2 overexpression does not affect anxiety-like behavior in either, juvenile R6/1 or WT mice

To examine whether the striatal overexpression of Foxp2 in the juvenile R6/1 and WT mice striatum could affect anxiety-like behavior we performed a plus maze test (Figure 31A). All groups spent similar percentage of the time in open arms (Figure 31B), and closed arms (Figure 31C) of the plus maze. Two-way ANOVA showed that there was neither genotype effect ($F_{(1,7)}$=0.0414; p=0.8445), nor treatment effect ($F_{(1,7)}$=0.0027; p=0.9596), nor interaction effect ($F_{(1,7)}$=1.329; p=0.2869), suggesting no differences between groups regarding anxiety-like behavior.

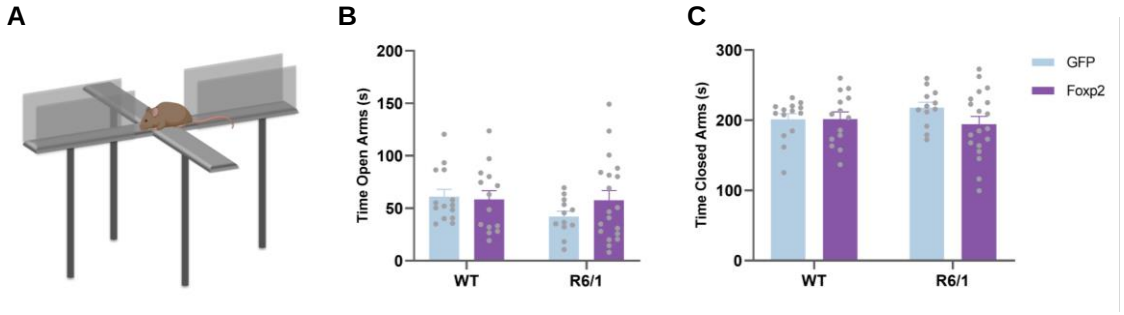


Figure 31. Transduced juvenile R6/1 mice and WT littermates' performance in the plus maze. (A) Plus maze apparatus. **(B)** Time spent in the open arms. **(C)** Time spent in the closed arms. Data were analyzed by two-way ANOVA test with genotype and treatment as factors. Data were expressed as (mean ± S.E.M) (n=14-19 animals per group).

3.4. Foxp2 treatment improves the impulsivity-phenotype in the juvenile R6/1 mice

To evaluate the effects of Foxp2 rescued levels in the striatum of R6/1 mice in impulsivity-like behavior, juvenile R6/1-GFP, R6/1-Foxp2, WT-GFP and WT-Foxp2 mice were subjected to the cliff avoidance jumping test (Figure 32A).

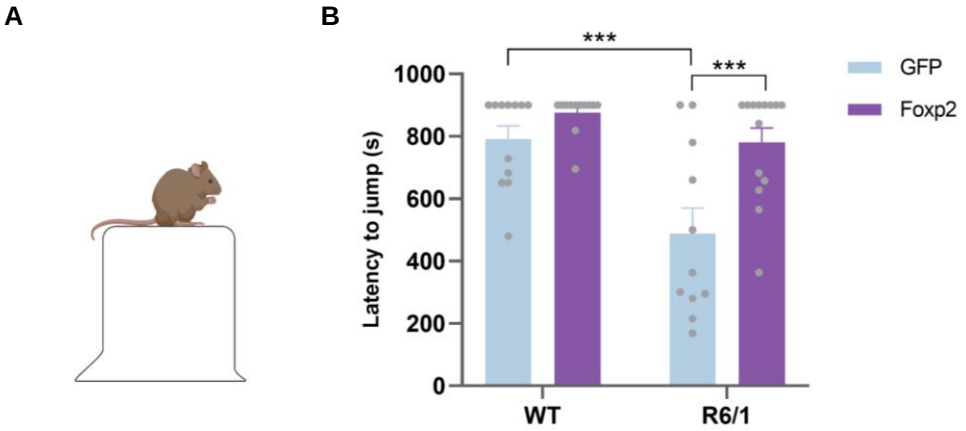


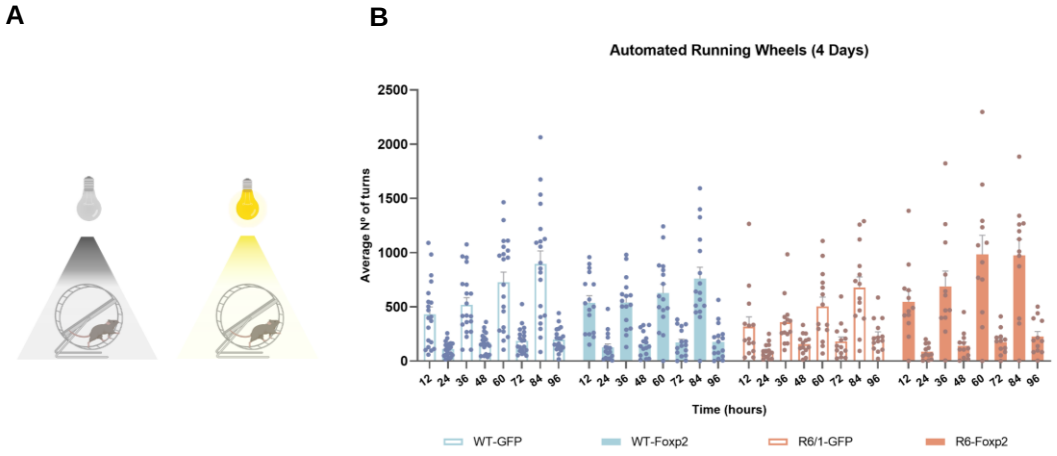
Figure 32. Transduced juvenile R6/1 mice performance in the cliff avoidance test. (A) Cliff avoidance jumping test. **(B)** Latency to jump out of the platform in the cliff avoidance jumping test. Data were analyzed

by two-way ANOVA test with genotype and treatment as factors. ***p < 0.001. Tukey's post hoc test was performed. Data were expressed as (mean ± S.E.M) (n=12-14 animals per group).

Two-way ANOVA revealed a genotype ($F_{(1,45)}$=15.26; p=0.0003), treatment ($F_{(1,45)}$=13.78; p=0.0006) and interaction effect ($F_{(1,45)}$=4.192; p=0.0465). Interestingly, juvenile R6/1-GFP mouse replicated previous impulsive-like behavior by spending less time in the round platform than WT-GFP (p=0.0010) as showed by Tukey's post hoc analysis. Tukey´s post hoc analyses yielded up that R6/1-Foxp2 mice spent more time in the round platform that R6/1-GFP (p=0.0010). Further, time spent by the R6/1-Foxp2 mice in the round platform reached similar levels to WT-GFP group (p=0.9990) (Figure 32B). All these data suggest that Foxp2 striatal overexpression in the R6/1 mice restored impulsivity levels.

3.5. Transduced juvenile R6/1 mice do not replicate altered locomotor circadian rhythms

To evaluate whether the striatal overexpression of Foxp2 in the juvenile R6/1 and WT mice striatum could modulate locomotor circadian rhythms, we assessed the free-running period of locomotor activity in all experimental groups for 4 days (Figure 33A). Regarding general activity cycle, two-way ANOVA showed time effect ($F_{(2.347,136.1)}$=99.63; p<0.0001) and interaction effect ($F_{(21,406)}$=2.274; p=0.0012), but group effect was not observed ($F_{(3,58)=}$1.410; p=0.2489). Tukey's pos hoc test did not reveal differences between groups (Figure 33B). With regard to the dark cycle, two-way ANOVA showed group ($F_{(3,236)=}$7.216; p=0.0001), and time effect ($F_{(3,236)}$=12.39; p<0.0001), but interaction was not observed ($F_{(9,236)=}$0.5065; p=0.8692) (Figure 33C). With respect to the light cycle, two-way ANOVA showed time effect ($F_{(3,239)=}$8.907; p<0.0001), but neither group ($F_{(3,239)=}$1.049; p=0.3715), nor interaction effect ($F_{(9,239)=}$0.3027; p=0.9734) was observed(Figure 33D). Unexpectedly, R6/1-GFP mice did not replicate the disrupted locomotor circadian rhythms previously displayed.



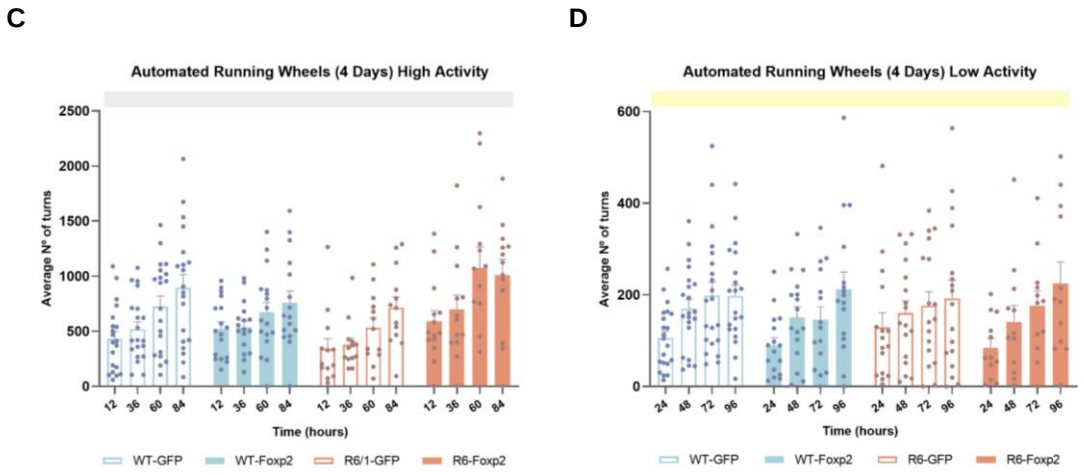


Figure 33. Measurement of free-running period in the transduced juvenile R6/1 mice in a light/dark cycle. (A) Running Wheels Paradigm in the light/dark cycle. **(B)** Free-running period for 4 days. **(C)** Free-running period during dark cycle. **(D)** Free-running period during light cycle**.** Data were analyzed by repeated measures ANOVA with genotype and time as factors. Data were expressed as (mean ± S.E.M). (n=16-21 animals per genotype).

However, Foxp2 overexpression seemed to have a differential effect by reducing the free-running periods of WT-Foxp2 and increasing the free-running periods of R6-Foxp2 during dark cycle. Overall, these data suggest that even under the lack of R6/1 mice phenotype, Foxp2 overexpression could regulates free-running periods during dark cycle.

3.6. Juvenile R6/1 mice show less aggressive-like behavior

To further investigate the psychiatric-like alterations of the juvenile R6/1 mouse we performed a Resident-Intruder paradigm designed to assess aggressive-like behavior in mice. Experimental mice groups were single-isolated for 4 days, and then exposed to a conspecific intruder in their home cage for 10 minutes. We were mainly focused in measuring social interaction (sniffing) (Figure 34A) and aggressive behavior (fighting) (Figure 34D). Regarding sniffing behavior, all the groups displayed similar latency to sniffing (Figure 34B). However, regarding sniffing duration, two-way ANOVA analysis indicated an interaction effect ($F_{(1,44)}$=6.337;p=0.0155), even when neither genotype ($F_{(1,44)}$=0.1302;p=0.7200), nor treatment effect ($F_{(1,44)}$=1.752;p=0.1924) were seen. Tukey's pos hoc analysis showed a significant difference between WT-GFP and WT-Foxp2 (p=0.0443) (Figure 34C). Interestingly, we discovered that R6/1-GFP mice were less aggressive than WT-GFP (Figure 34E). Less R6/1-GFP mice initiated a fight and the latency to start a fight also took longer ($F_{(1,44)}$=4.252;p=0.0451), compared to WT as indicated by two-way ANOVA genotype effect. Nevertheless, even when two-way ANOVA showed an interaction effect

($F_{(1,44)}$=4.368;p=0.0424), treatment effect was not seen ($F_{(1,44)}$=0.00002;p=0.9869). Tukey's multiple comparison showed that juvenile WT-GFP latency to fight was significantly different to R6/1-GFP (p=0.0303), but not to R6/1-Foxp2 (p=0.4593). Similarly, the duration of the fight of the R6/1 mice was shorter ($F_{(1,44)}$=9.459;p=0.0036) compared to WT as indicated by two-way ANOVA genotype effect, but neither interaction ($F_{(1,44)}$=1.480;p=0.2303), nor treatment effect ($F_{(1,44)}$=0.9419;p=0.3371) were seen (Figure 34F). All these data suggest that R6/1 displayed less aggressive behavior than WT mice, and that rescue of Foxp2 levels could modulate these alterations.

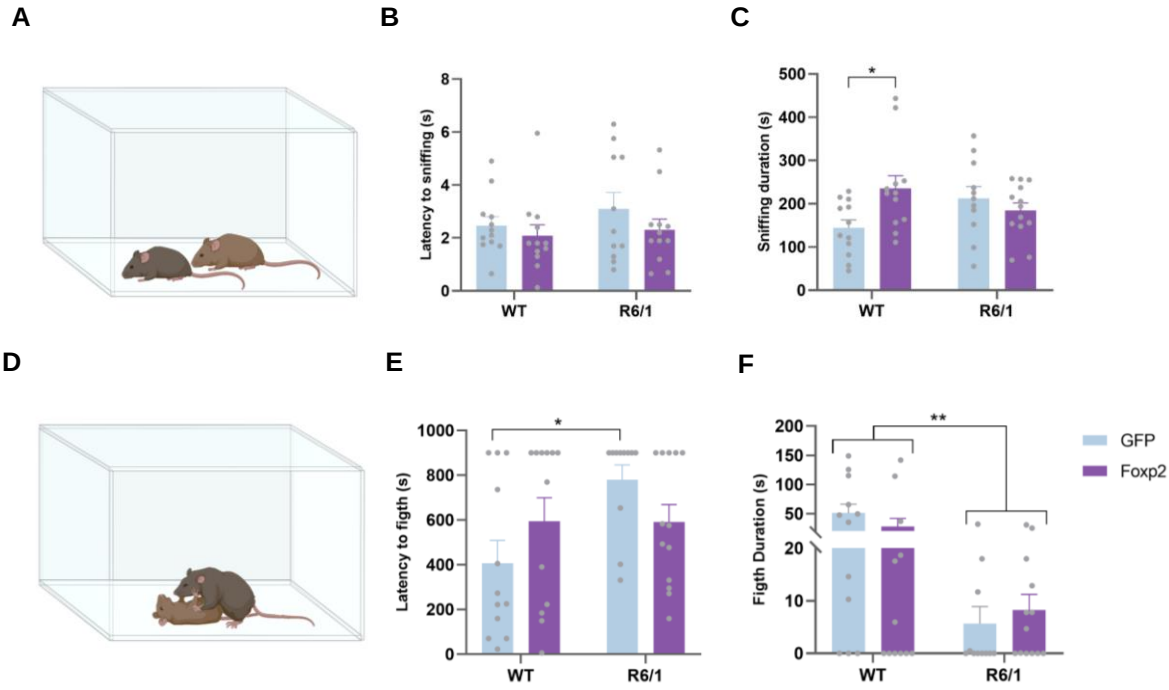


Figure 34. Measurement of aggressive-like behavior in the transduced juvenile R6/1 mice. (A) Resident-Intruder Paradigm Sniffing Behavior. **(B)** Latency to sniffing. **(C)** Duration of the sniffing. **(D)** Resident-Intruder Paradigm Fight Behavior. **(E)** Latency to fight. **(F)** Duration of the fight. Data were analyzed by a two-way ANOVA with genotype and treatment as factors. *p < 0.05, **p < 0.01. Data were expressed as (mean ± S.E.M) (n=12-14 animals per group).

3.7. Foxp2 treatment prevents loss of spine density in the juvenile R6/1 mice

To elucidate whether Foxp2 overexpression correlated with changes in structural plasticity in the striatum, we next analyzed the dendritic spine density in Golgi-impregnated striatal neurons in Foxp2 treated mice and controls. The dendritic spine density in striatal neurons from R6/1-GFP mice was reduced compared to WT mice, indicated by a signification of genotype factor in the two-way ANOVA analysis ($F_{(1,302)}$=9.678; p=0.0020). Two-way

ANOVA also showed a treatment ($F_{(1,302)}$=9.728; p=0.0020), and interaction effect ($F_{(1,302)}$=14.65; p=0.0002). Sidak's post hoc analyses revealed that R6/1-GFP mice have a significant lower spine density compared to WT-GFP (p<0.0001) and WT-Foxp2 (p=0.0003) respectively. Additionally, R6/1-Foxp2 mice had also a significant greater density than R6/1-GFP (p<0.0001) indicating that striatal Foxp2 overexpression delayed the onset of dendritic spine pathology in the striatum of R6/1 mice. Furthermore, no differences were seen between R6/1-Foxp2 compared to WT-GFP (p>0.9999) and WT-Foxp2 groups (p=0.9967), suggesting that Foxp2 treatment completely rescued striatal spine density loss in the juvenile R6/1 mouse (Figure 35A, B).

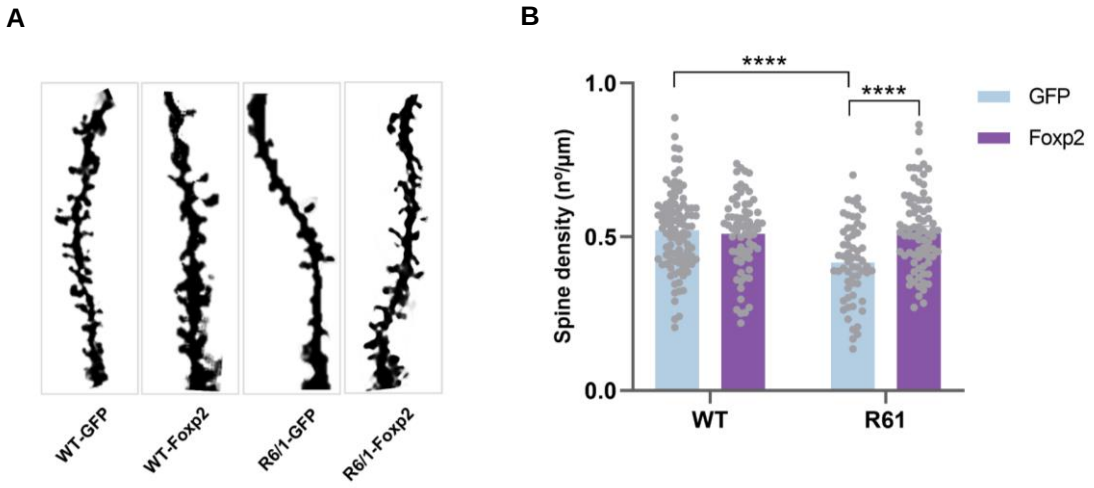


Figure 35. Spine dendritic analysis in the transduced juvenile R6/1 mice. (A) Representative photomicrographs showing striatal dendrites of WT-GFP, WT-Foxp2, R6/1-GFP and R6/1-Foxp2. **(B)** Histogram shows quantitative analysis of dendritic spine density per micrometer. Data were analyzed by two-way ANOVA test with genotype and treatment as factors. ****p < 0.0001. Sidak's post hoc test was performed. Data were expressed as (mean ± S.E.M) (~300 dendrites; n=4-5 animals per group).

3.8. Foxp2 overexpression restores downregulated and upregulated striatal proteins expression levels

As early behavioral and synaptic changes showed by the juvenile R6/1 mice were improved by Foxp2 overexpression, we next focused in identify the underlying molecular alterations of these deficits, and whether Foxp2 overexpression could modulated its. We aimed to screening protein expression in the striatum of transduced juvenile R6/1 mice and WT littermates using a mass-spectrometry assay. As expected, according to presymptomatic stage of the R6/1 mouse model, we found subtle changes in protein expression. A total of 35 proteins were differentially expressed between juvenile R6/1-GFP and WT-GFP (p < 0.05), 19 of the aberrantly regulated proteins were downregulated, and 16 were upregulated. Most

of the altered proteins were related with cytoskeleton dynamics such as trafficking, actin filament and GTPase activity. Interestingly, Arhgap4, Sez6l2 and Tceal1 were associated with schizophrenia, Aldh1a, Dpp6, Dpysl4, Scarb2 and Sez6l2 were associated with risk-taking behavior, while Arhgef10l was related to insomnia (Figure 36A). Surprisingly, most of the aberrantly regulated proteins were restored in the R6/1 mice after Foxp2 overexpression (Figure 36B), only 2 altered proteins were not changed, whereas 6 new proteins were altered by Foxp2 overexpression (Figure 36C).

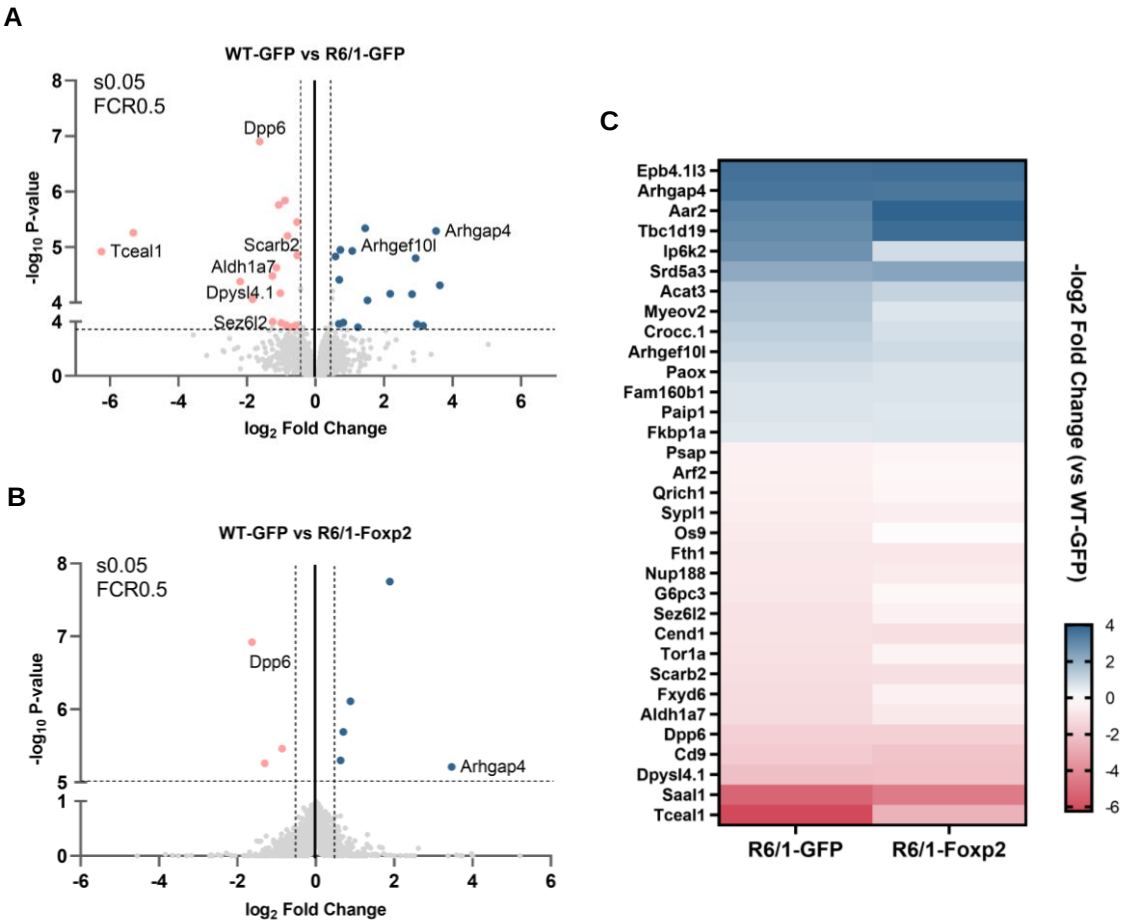


Figure 36. Molecular analysis of the transduced juvenile R6/1 mice striatum. (A) Histogram shows downregulated (red) and upregulated proteins (blue) of R6/1-GFP mice striatum respect to WT-GFP mice. **(B)** Histogram shows downregulated (red) and upregulated proteins (blue) of R6/1-Foxp2 mice striatum respect to WT-GFP mice. **(C)** Heat map shows clusters of downregulated (red) and upregulated proteins (blue) of R6/1-GFP and R6/1-Foxp2 mice striatum respect to WT-GFP mice. Cutoffs of ±0.5-fold change and $p < 0.05$.

3.9. GABAergic and dopaminergic synaptic markers were unaltered by striatal Foxp2 overexpression

Since some of the psychiatric alterations observed in juvenile R6/1 animals such as aggression or impulsivity are related to GABAergic and dopaminergic neurotransmission (Jupp et al., 2013), we aimed to explore if the behavioral psychiatric-like deficits could be related to synaptic or circuits alterations, and to study whether Foxp2 could regulates such disturbances. We first analyzed protein levels of $GABA_A\alpha1$, $GABA_A\alpha2$ and $GABA_A\beta3$ in striatal samples of treated and control animals. Two-way ANOVA analysis revealed no significant changes in striatal $GABA_A\alpha1$, $GABA_A\alpha2$ and $GABA_A\beta3$ protein levels between groups (Figure 37A, B, C). We next analyzed striatal samples for components of dopaminergic pathway as p-PKA cat, p-PKA substrates and tyrosine hydroxylase which plays a role in catecholamine biosynthesis. Two-way ANOVA analysis showed no significant changes between groups (Figure 37D, E, F).

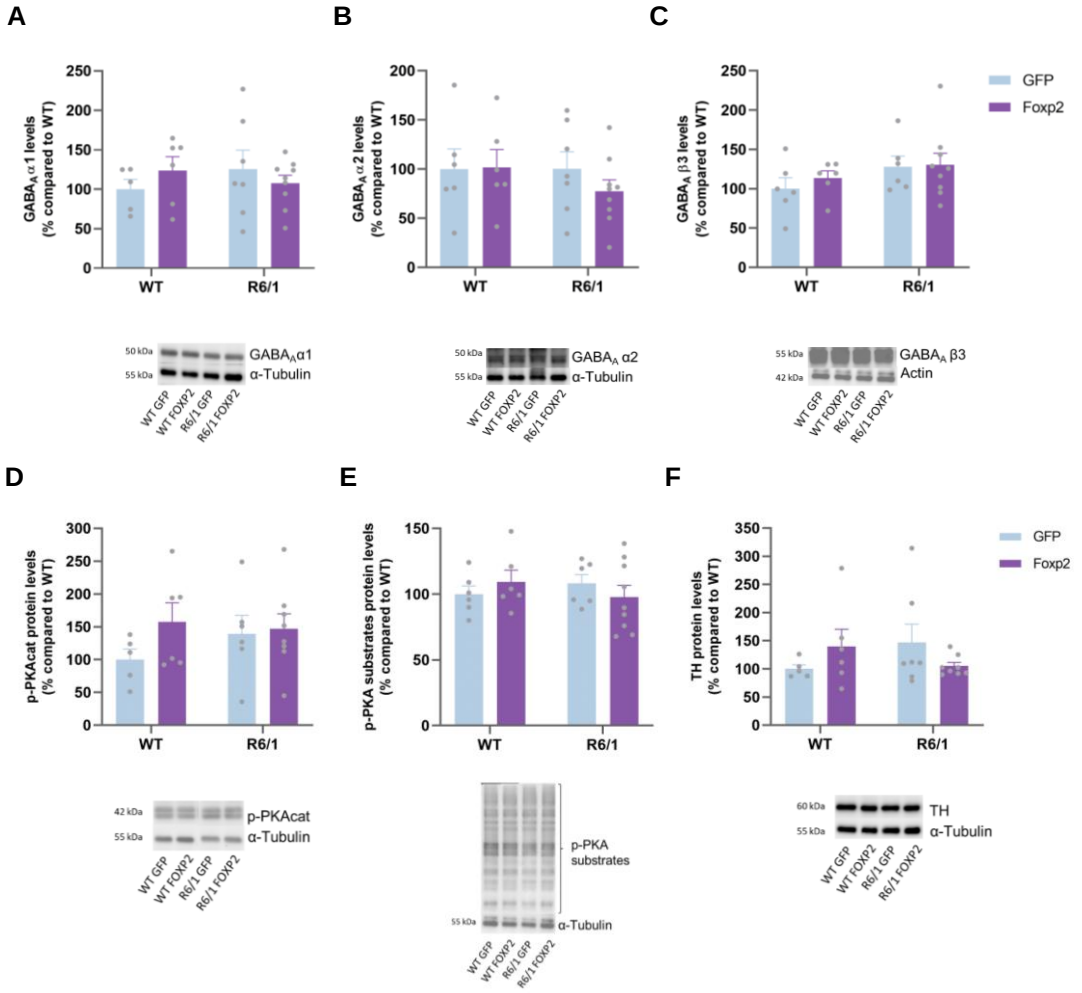


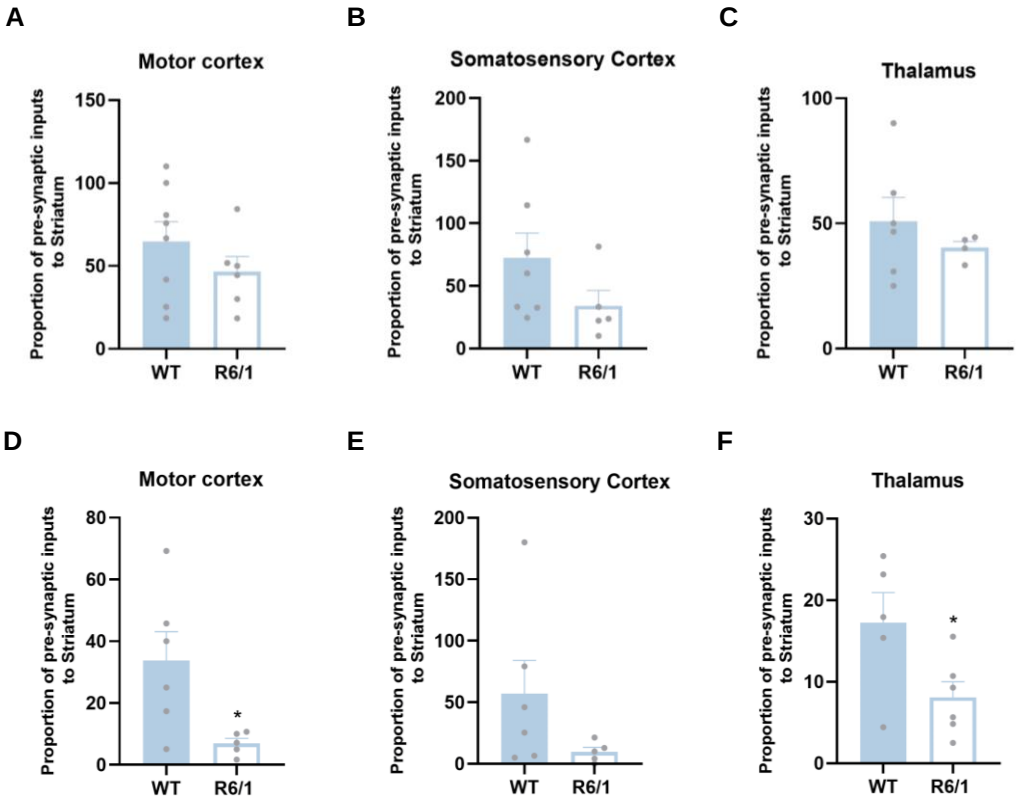
Figure 37. Expression of GABAergic and dopaminergic synaptic markers in the transduced juvenile R6/1 mice. Densitometric analysis showing protein levels of **(A)** $GABA_A\alpha1$ protein levels. **(B)** $GABA_A\alpha2$ protein levels. **(C)** $GABA_A\beta3$ protein levels. **(D)** p-PKAcat protein levels. **(E)** p-PKA substrates protein levels. **(F)** TH protein levels in WT and R6/1 striatum of treated and control animals. Protein levels were normalized with tubulin or actin as loading control. Representative immunoblots are shown below. Data were analyzed by two-way ANOVA with genotype and treatment as factors. Data were expressed as (mean ± S.E.M) (n=7-9 animals per group).

4. Assessment of striatal afferent pathways in the R6/1 mouse model

As our previous data showed Foxp2 overexpression in juvenile R6/1 mice striatum has shown an important role in regulating synaptic plasticity. As thalamus is also a Foxp2-enriched region, we hypothesize that Foxp2 could regulates thalamostriatal connections in a similar way as modulation of corticostriatal pathway and its sensorimotor-related responses (French et al., 2012; Groszer et al., 2008). Thus, in this section, we aimed to assess striatal afferents pathway in presymptomatic and symptomatic stages. We particularly aimed to focus in thalamostriatal connections, which have been poorly addressed in HD, and also study its relationship with HD-sensoriomotor phenotypes, and ultimately to analyze the contribution of Foxp2 in these alterations.

4.1. Cortical and thalamic synaptic inputs to the striatum are altered in R6/1 mouse

To assess brain network connectivity in R6/1 mice we used a monosynaptic circuit tracing system in 6-week-old (presymptomatic) and 12-week-old R6/1 mice (early symptomatic) and age-matched WT controls, that allowed us to study a whole-brain mapping of the main brain regions that directly targeted striatum as motor and somatosensory cortex and thalamus. At 6-week-old, the proportion of pre-synaptic inputs from motor cortex (t_{12}=1.154, p=0.1354), somatosensory cortex (t_{10}=1.498, P=0.1651) and thalamus (t_8=0.8638, p=0.4128) of R6/1 mice was not significantly different to WT controls (Figure 38A, B, C). At 12-week-old, R6/1 mice showed a significant smaller proportion of presynaptic inputs from cortex (t_9=2.577, p=0.0149) (Figure 38D, G, H), and thalamus (t_9=2.330, p=0.0224) (Figure 38F, K, L), but not from somatosensory cortex (t_9=1.573, p=0.1503) compared to WT controls (Figure 38E, I, J).



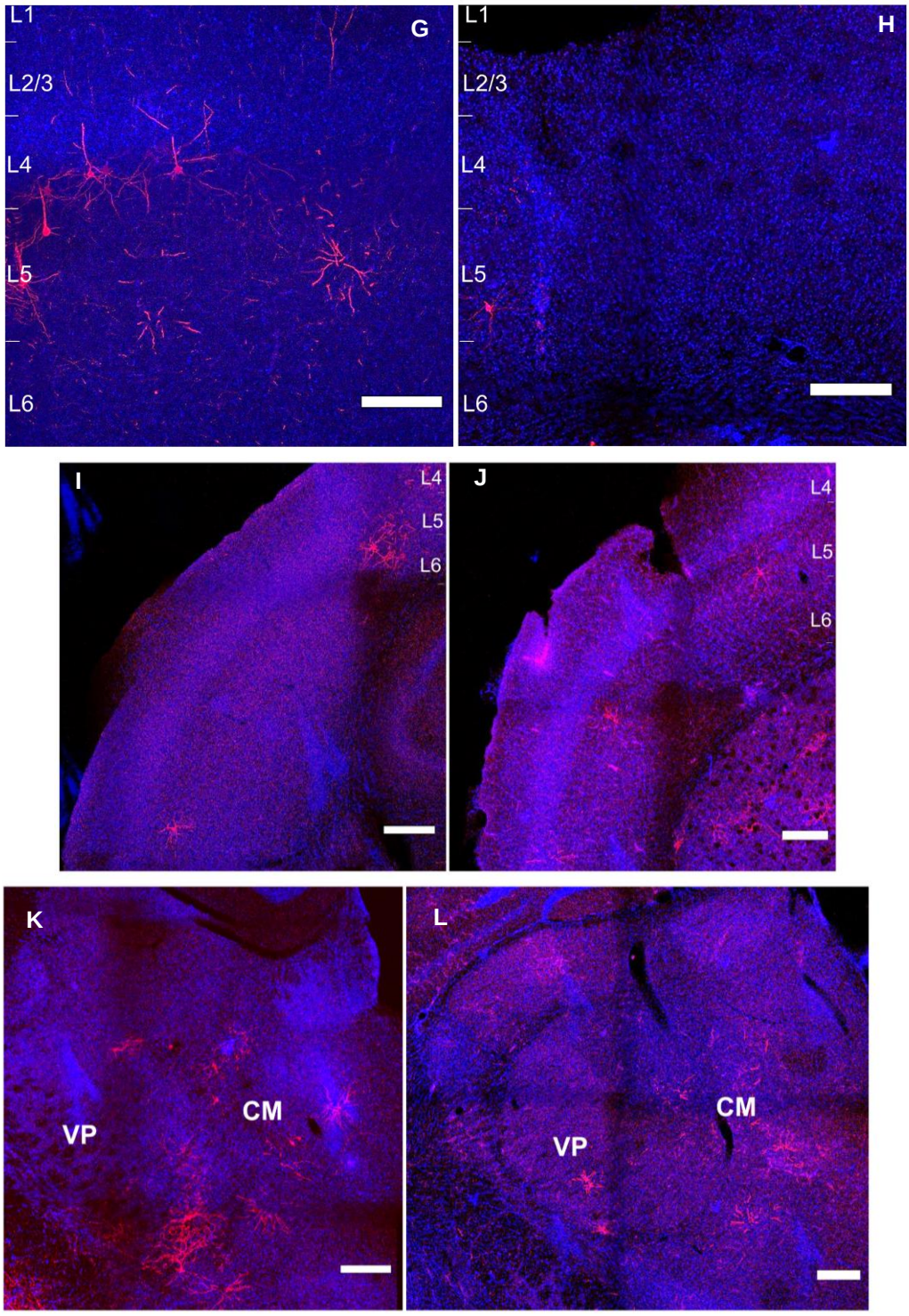


Figure 38. Cortical and thalamic synaptic inputs to striatum of the R6/1 mouse. Histograms show quantitative analysis of proportion of pre-synaptic inputs to 6-week-old R6/1 mice striatum from **(A)** Motor cortex. **(B)** Somatosensory cortex. **(C)** Thalamus. Histograms show quantitative analysis of proportion of pre-synaptic inputs to 12-week-old R6/1 mice striatum from **(D)** Motor cortex. **(E)** Somatosensory cortex. **(F)** Thalamus. Representative micrographs of pre-synaptic inputs to 12-week-old R6/1 mice striatum from **(H)** Motor Cortex. **(J)** Somatosensory Cortex. **(L)** Thalamus. Representative micrographs of pre-synaptic inputs to 12-week-old WT mice striatum from **(I)** Motor Cortex. **(K)** Somatosensory Cortex. **(M)** Thalamus. Scale bar: 250μm. Data were analyzed by Student's two-tailed t test. *$p < 0.05$. Data were expressed as (mean ± S.E.M) (n=6-8 animals per group for 6-week-old mice/ n=5-6 animals per group for 12-week-old mice).

5. Expression and distribution of Foxp2 in the thalamus of R6/1 mice

5.1. Foxp2 protein levels are decreased in the thalamus of presymptomatic R6/1 mouse

To examine whether the endogenous Foxp2 protein levels were perturbed in the R6/1 mouse model, Foxp2 protein levels were analyzed in thalamic extracts obtained from R6/1 mice and WT controls. Thalamic samples were analyzed at different symptomatic stages: asymptomatic stage (8 weeks), early symptomatic stage (12 weeks), and late symptomatic stage (20 weeks). Interestingly, western blot analysis revealed that Foxp2 expression was significantly altered at 8 weeks (t_{10}=3.016, p=0.0130), 12 weeks (t_{10}=2.357, p=0.0402) and 20 weeks (t_{10}=4.288, p=0.0016) in the transgenic R6/1 mice striatal tissue compared to the WT mice. (Figure 39A).

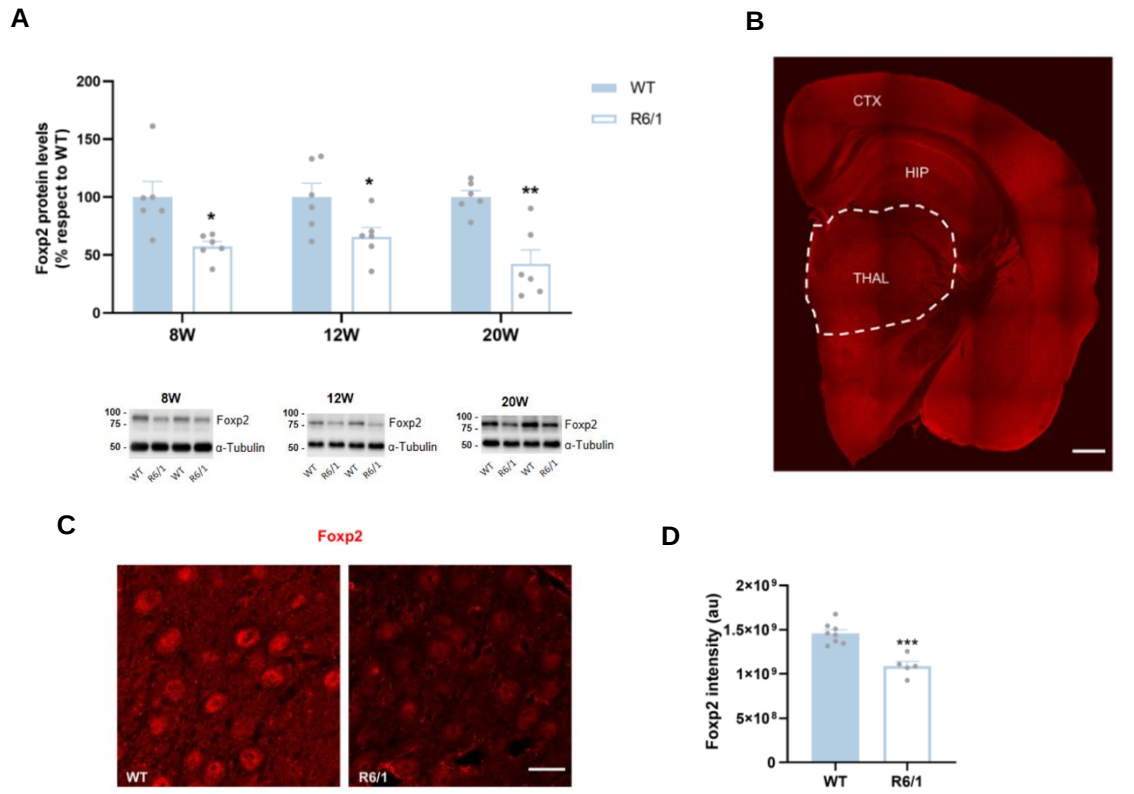


Figure 39. Expression and distribution of endogenous Foxp2 in thalamus of R6/1 mice. (A) Densitometric analysis showing protein levels of Foxp2 in WT and R6/1 thalamus at 8, 12 and 20 weeks. Protein levels were normalized with tubulin as loading control. Representative immunoblots are shown below. **(B)** Photomicrograph showing Foxp2 distribution in a WT brain mouse. Scale bar: 500µm. **(C)** Representative photomicrographs (high magnification) showing Foxp2 nuclei expression and localization in the thalamus of R6/1 mice and WT controls. Scale bar: 10µm. **(D)** Histogram shows quantification of the average of Foxp2-positive nuclei in the thalamus. Data were analyzed by Student's two-tailed t test. *p < 0.05, **p < 0.01, ***p < 0.001. Data were expressed as (mean ± S.E.M) (n=6 per genotype/Western Blot; n=5-8 mice per genotype/Immunofluorescence).

To further investigate if the reduction of Foxp2 levels was restricted to different thalamic nuclei or, in contrast, was homogenous in the whole thalamus, we next performed an immunofluorescence against Foxp2 in 16-week-old R6/1 mice and WT age-matched controls. We choose to investigate the levels of Foxp2 in the 16-week-old R6/1 mice because is a well-characterized symptomatic age, in which described behavioral deficits are consistent between studies. Also, based on the expression and distribution of Foxp2 in the R6/1 mouse at this age, we will select the specific region or nuclei for the recovery of Foxp2 levels. Foxp2 intensity was measured in coronal sections of the thalamus (Figure 39B). Interestingly, we found a significant homogeneous reduction of Foxp2 protein levels in R6/1 thalamus compared to WT littermates (t_8=2.654, p=0.0291) (Figure 39C, D).

5.2. Foxp2 shows a weak colocalization with mHtt in the thalamus of presymptomatic R6/1 mice

Even when intracellular aggregates are a common feature of striatum or cortex regions (Naver et al., 2003), we considered to examine whether perturbed levels of endogenous Foxp2 might be due to a Foxp2-mHtt interaction. Therefore, we performed an immunofluorescence against Foxp2 and EM48 in coronal thalamic sections of pre-symptomatic 8-week-old R6/1 mouse and WT controls. As expected, we found diffuse nuclear staining and few immunolabeled nuclear inclusions in the thalamus of R6/1 mouse (Figure 40). Also, it seems that Foxp2 staining presents a weak colocalization with mHtt, at least, at this stage.

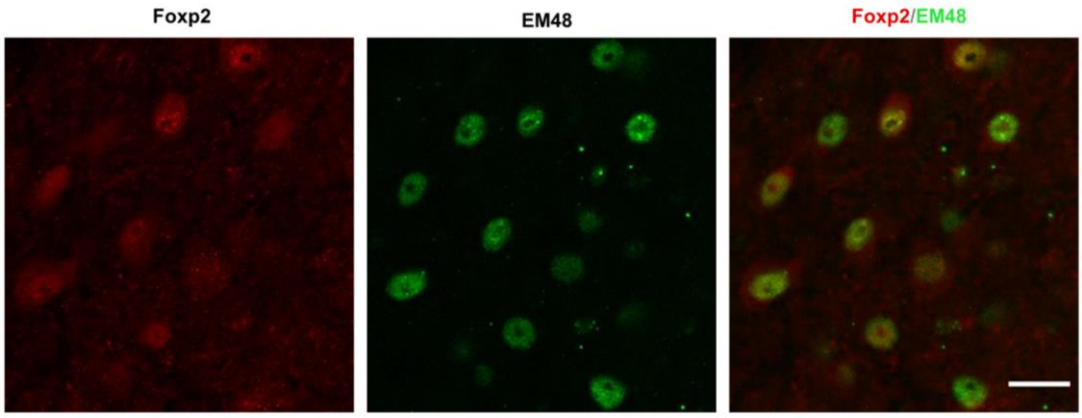


Figure 40. Foxp2 colocalization with mHtt in the R6/1 mice thalamus. (A) Representative photomicrographs (high magnification) showing Foxp2 nuclei expression and EM48 labelling in the thalamus of R6/1 mice and WT controls. Scale bar: 20μm.

6. Normalization of Foxp2 levels in symptomatic R6/1 mouse thalamus

To address whether a Foxp2 rescue approach could restore motor-sensory deficits previously described in the R6/1 mouse model (Mazarakis et al., 2005; Puigdellívol et al., 2015), we choose to rescue the levels of Foxp2 in the ventrolateral thalamus because it is consisted of the ventral posterior nucleus that projects to the dorsolateral striatum, which is involved in motor coordination and learning consolidation (Cataldi et al., 2021; Díaz-Hernández et al., 2018). In addition, the ventral posterior nucleus targets the layer 4 of somatosensory cortex (barrel cortex), which processes neuronal information of whisker-sensory and tactile perception in mice (Guo et al., 2020). Therefore, we transduced the ventrolateral thalamus of 12-week-old R6/1 mice and WT mice with an AAV9 designed to overexpress Foxp2. R6/1 and WT mice control groups were injected with an AAV9 expressing only GFP. We waited for 4 weeks until the virus expression was stable and then subjected the animal to an array of behavioral test (Figure 41A, B).

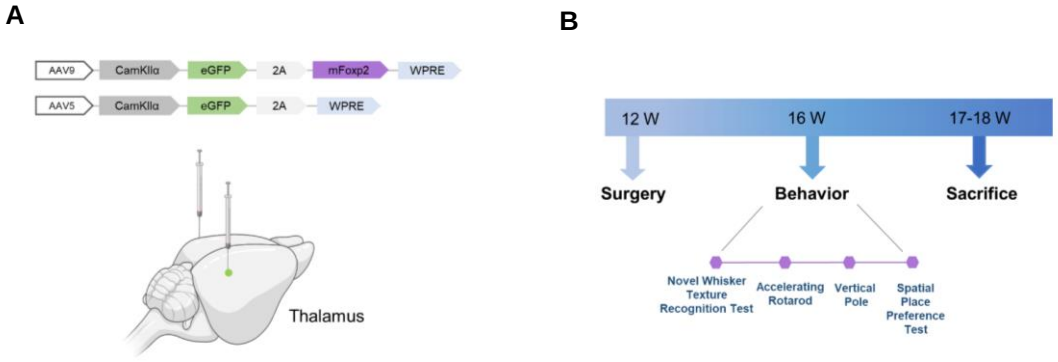


Figure 41. Experimental Design of Foxp2 Thalamus Overexpression. **(A)** Viral constructs injected in the ventrolateral thalamus of R6/1 and WT mice. **(B)** Timeline.

6.1. Verification of Foxp2-Overexpression in the thalamus of symptomatic R6/1 mice

To validate the overexpression of Foxp2 in the symptomatic 16-week-old R6/1 mice and WT aged-matched controls we performed an immunofluorescence against Foxp2 and GFP signal. A double labelling Foxp2-GFP revealed viral transduction in the ventrolateral thalamus (Fig 42A). Two-way ANOVA analysis showed significant differences between R6/1 and WT control mice ($F_{(1,155)}$=32.75; p<0.0001), corroborating the Foxp2 downregulation previously observed in mutant mice. Foxp2 overexpression in the thalamus was confirmed by a significant difference in treatment factor ($F_{(1,155)}$=100.3; p<0.0001), and interaction was not seen ($F_{(1,155)}$=0.7112; p=0,4003). Despite the lack of interaction, Tukey's multiple comparison test showed that Foxp2 intensity in R6/1-Foxp2 was significantly greater than in R6/1-GFP (p<0.0001) (Figure 42B, C).

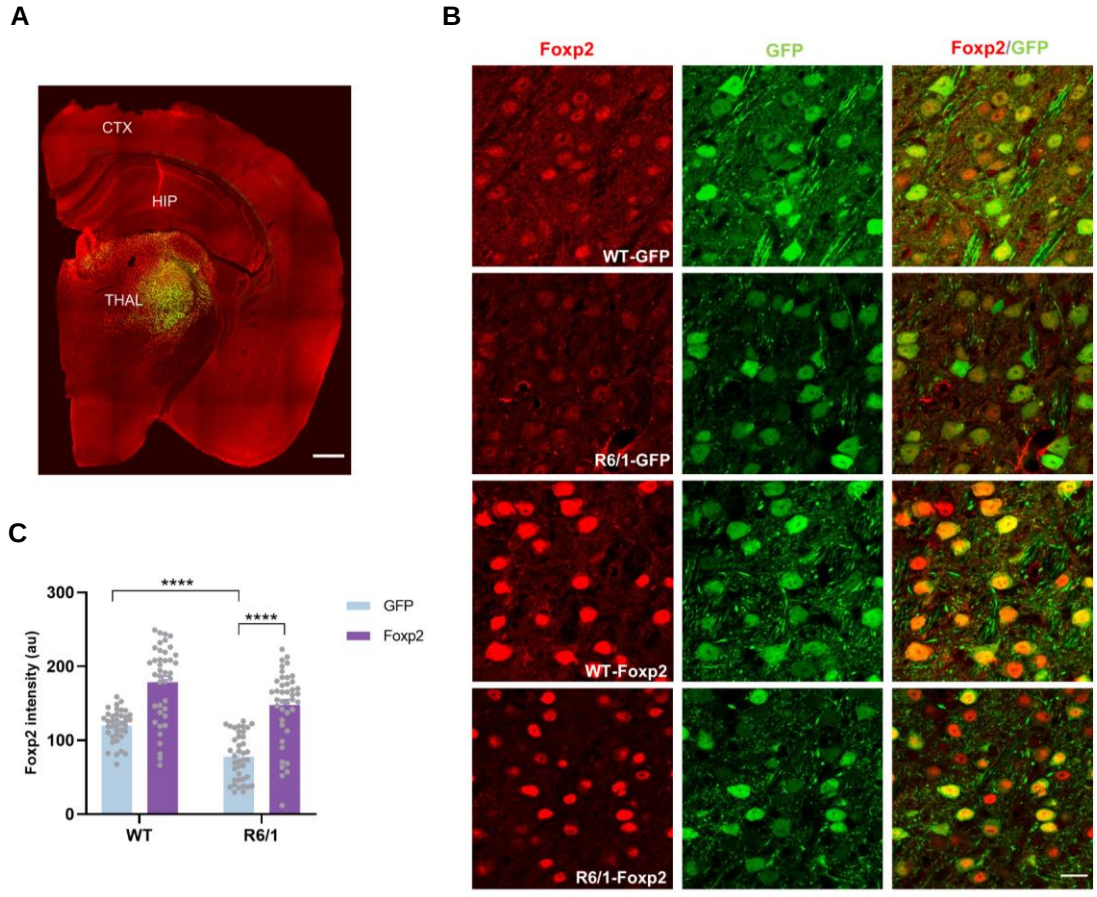


Figure 42. Expression and distribution of Foxp2 in the transduced symptomatic R6/1 mice (A) Representative photomicrograph of site of injection of AVV9 in the ventrolateral thalamus. Scale bar: 500µm. **(B)** Representative photomicrographs (high magnification) showing double labelling of Foxp2 and GFP in the thalamus of WT-GFP, R6/1-GFP, WT-Foxp2 and R6/1-Foxp2. Scale bar: 10µm. **(C)** Histogram shows quantification of the average of Foxp2-positive nuclei in the thalamus. Data were analyzed by two-way ANOVA with genotype and treatment as factors. Tukey's post hoc test was performed. Data were expressed as (mean ± S.E.M) (~40 nuclei per group; n=4 animals per group).

6.2. Foxp2 overexpression in the ventrolateral thalamus fully recovers whisker-sensory disturbances in the R6/1 mouse

We subjected 16-week-old R6/1-GFP, R6/1-Foxp2, WT-GFP and WT-Foxp2 mice to a battery of motor-sensory test (Figure 43A). As referred before, transgenic R6/1 mouse model shows sensory deficits in a barrel cortex-dependent sensory-discrimination learning task (Mazarakis et al., 2005). As barrel cortex-dependent sensory-discrimination depends on thalamic-cortical pathway (El-Boustani et al., 2020), we aimed to check whether the restoration of Foxp2 levels in the thalamus could mitigate these alterations. Novel whisker-dependent texture discrimination test was conducted as previously reported (Wu et al., 2013) (Figure 43B). We first measured locomotor and exploratory activity during 2 days of habituation in the open field. Only data from day 1 of habituation (Figure 43C) is shown as representative of the following parameters: distance, mean speed, and time in the center. All experimental groups traveled similar distances (Figure 43D), at similar speed ratio (Figure 43E). Also, all experimental groups spent similar times in the center of the open field, suggesting similar levels of anxiety-like behavior (Figure 43F). Similarly, only data from day 1 of habituation is shown as representative of the following parameters: supported rearing (exploratory behavior) and unsupported rearing (emotional-like behavior) (Sturman et al., 2018) indicating the levels of exploratory activity. Two-way ANOVA genotype effect showed significant differences between WT and R6/1 groups regarding supported rearing ($F_{(1,53)}$=10.68; p=0.0019) (Figure 43G), and unsupported rearing ($F_{(1,52)}$=18.94; p<0.0001) (Figure 43H). On the third testing day, during training phase, all groups explored the two similar smooth-textured objects in the arena. The two smooth-textured objects were similarly explored without preference by all groups (Figure 43I). Interestingly, during the testing phase, R6/1-Foxp2 displayed an improved sensory-whisker discrimination as described by two-way ANOVA with significant object effect ($F_{(1, 94)}$=23.24; p<0.0001) and interaction effect ($F_{(3, 94)}$=7.940 p<0.001), even when no group effect was seen ($F_{(3,94)}$=7.769e-022); p>0.9999). Bonferroni's pos hoc analyses revealed that WT-GFP (p=0.0012), WT-Foxp2 (p=0.0085) and R6/1-Foxp2 mice (p<0.0001) could discriminate between the familiar smooth texture and the novel rough texture, but not R6/1-GFP mice (p=0.3428) (Figure 43J). These results indicate that Foxp2 overexpression in the ventrolateral thalamus of R6/1 mice fully and specifically recovered whisker dependent sensory discrimination.

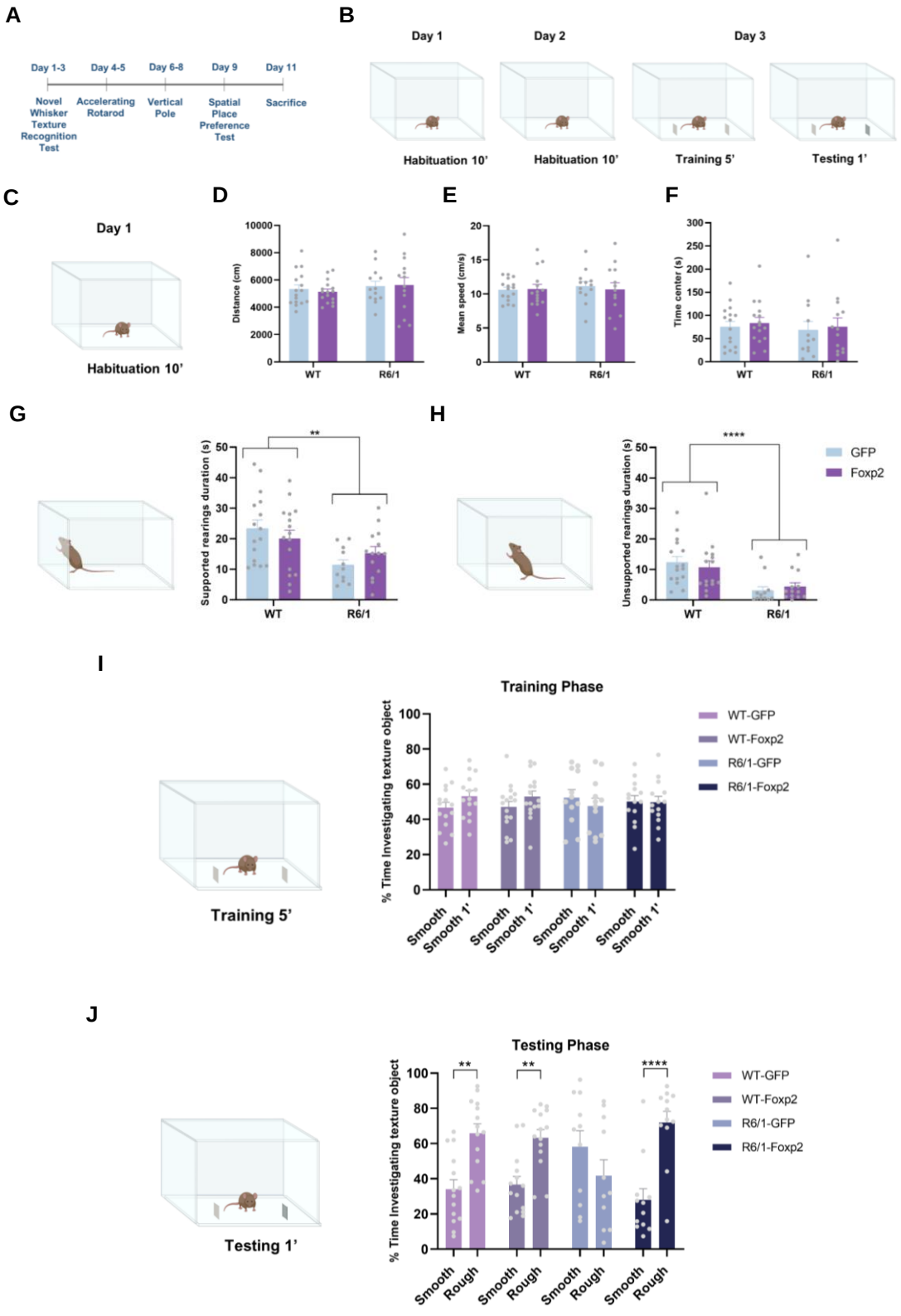


Figure 43. Symptomatic R6/1 mice performance in a barrel cortex-dependent sensory-discrimination learning task. (A) Battery of sensory-motor behavioral tests. **(B)** Novel Whisker Texture Discrimination Task (NWTDT). **(C)** Day 1 of habituation in the open field. **(D)** Distance. **(E)** Mean speed. **(F)** Time in the center. **(G)** Supported rearing. **(H)** Unsupported rearing. **(I)** % Time investigating texture object during training phase. **(J)** % Time investigating texture object during testing phase. Data were analyzed by two-way ANOVA with object and group as factors. Bonferroni's post hoc test was performed. **p < 0.01, ****p < 0.0001. Data were expressed (as mean ± S.E.M) (n=12-16 animals per group).

6.3. Foxp2 overexpression in the ventrolateral thalamus restores motor learning and coordination in the R6/1 mouse

Motor learning and coordination is severely affected in the R6/1 mouse model as previously described (Puigdellívol et al., 2015). To evaluate whether restoration of Foxp2 levels in the ventrolateral thalamus could alleviate motor deficits, all experimental groups were subjected to an accelerated rotarod test, and latency to fall was measured. Latency to fall from the rod was decreased in R6/1-Foxp2 mice reaching similar level to WT mice. Repeated measures ANOVA showed significant effects of mice group ($F_{(3,26)}$=4.039; p=0.0175), time ($F_{(2.461,63.97)}$=10.61, p<0.0001), even when no interaction effect was seen ($F_{(21,182)}$=0,9875; p=0.4808). Moreover, Tukey's post-hoc analyses showed significant differences between WT-GFP and R6/1-GFP (p<0.0001), and between R6/1-GFP and R6/1-Foxp2 (p<0.0001) (Figure 44). These data suggest that recovery of Foxp2 levels fully corrected motor learning and coordination impairments observed in R6/1 mice.

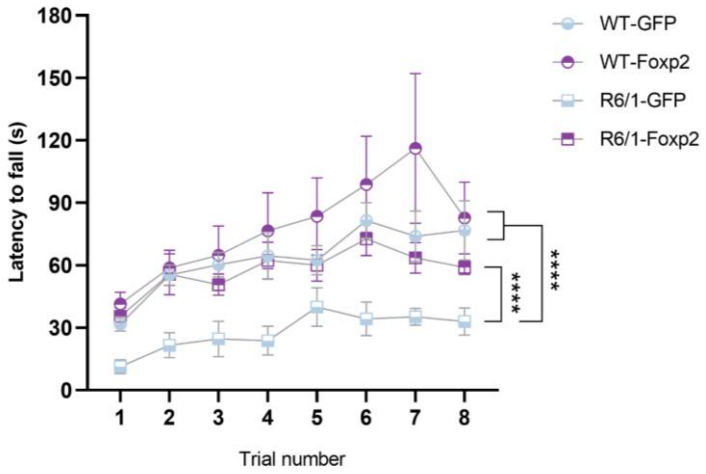


Figure 44. Motor performance of the thalamus transduced R6/1 mice. (A) Latency to fall in the accelerating rotarod task. Data were analyzed by repeated measures ANOVA with group and time as factors. Tukey's post hoc test was performed. ****p < 0.0001. Values are expressed as (mean ± S.E.M.) (n=6-9 animals per group).

6.4. Foxp2 overexpression in the ventrolateral thalamus does not restore impaired performance of R6/1 mice in the vertical pole test

To further investigate the effects mediated by Foxp2 recovery levels in thalamus, mice motor coordination in the turnover behavior was also evaluated in the vertical pole task. Both groups, R6/1-GFP and R6/1-Foxp2 mice, displayed longer latencies to turn ($F_{(1,54)}$=7.175; p=0.0098) (Figure 45A), longer latencies to go down ($F_{(1,54)}$=37.13; p<0.0001) (Figure 45B), and higher scores in the total time spent in the pole ($F_{(1,54)}$=26.89; p<0.0001) (Figure 45C), compared to WT mice group indicated by two-way ANOVA analysis genotype effect. No

treatment, nor interaction effect indicated that Foxp2 therapy was not able to improve R6/1 mouse alterations.

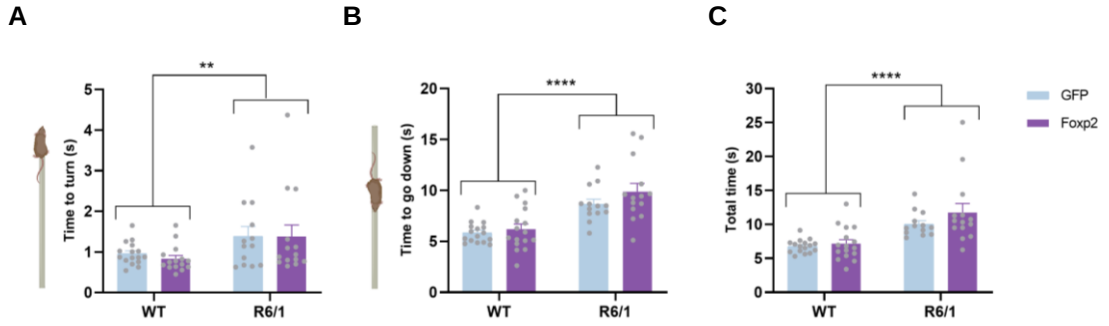


Figure 45. Symptomatic R6/1 mice performance in a vertical pole task. (A) Time to turn. **(B)** Time to go down. **(C)** Total time. Data were analyzed by two-way ANOVA with genotype and treatment as factors. **p < 0.01, ****p < 0.0001. Data were expressed as (mean ± S.E.M) (n=14-16 animals per group).

6.5. Symptomatic R6/1 mice show a similar performance in a tactile perception test than WT controls

To further investigate the range of sensory deficits in the symptomatic R6/1 mice and the effects of Foxp2 thalamic overexpression, we finally subjected the experimental groups to the spontaneous preference place test (Figure 46A). Whisker-trimmed mice were allowed to explore the open field square box containing two different textures (smooth and rough). Since mice seems to prefer rough texture over smooth ones (Manita et al., 2015) the time spent on a rough-textured place was a measure for the tactile perception performance. The percentages of time in the rough-textured place across the groups did not reach significant values (Figure 46B, C).

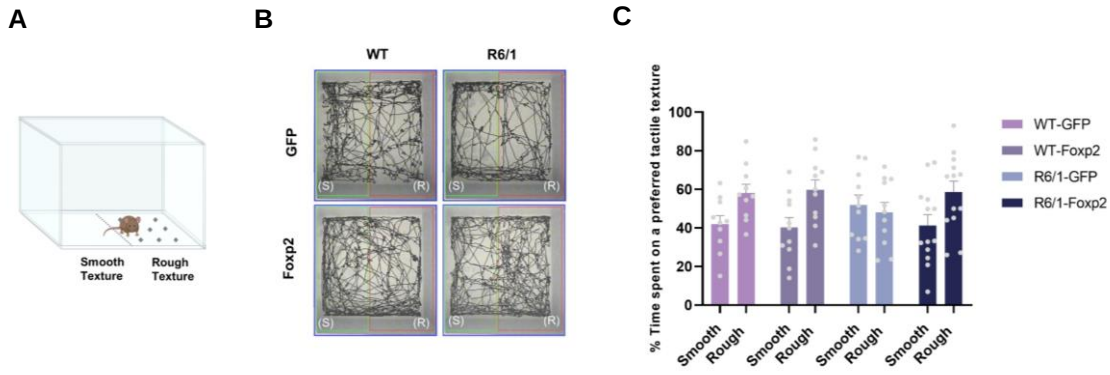


Figure 46. Symptomatic R6/1 mice performance in the spontaneous preference place test. (A) Spontaneous preference place test. **(B)** Representative images of path mice in the arena. **(C)** % Time spent on a preferred tactile texture. Data were analyzed by two-way ANOVA with genotype and object as factors. Data were expressed as (mean ± S.E.M) (n=10-13 animals per group).

Two-way ANOVA showed that there was neither genotype effect ($F_{(3,82)}$=97.416e-022; p>0.9999), nor interaction effect ($F_{(3,82)}$=2.140; p=0.1015). Interestingly, an object effect ($F_{(1,82)}$=9.228; p=0.0014) was observed. Altogether, these data suggest the absence of tactile disturbances in the R6/1 mice.

6.6. Foxp2 overexpression in the ventrolateral thalamus significantly corrects striatal dendritic spine loss in R6/1 mice

To further investigate whether improvement of motor deficits by Foxp2 overexpression in the ventrolateral thalamus correlated with structural plasticity changes, we analyzed dendritic spine density in Golgi-impregnated dorsal striatal neurons. Dendritic spine density was reduced in dorsal striatal neurons from R6/1 compared to WT mice, as previously described (Spires et al., 2004). Foxp2 overexpression in the thalamus increased the spine density in R6/1 mice striatum, without changing dendritic spine density in WT control, as indicated by two-way ANOVA with genotype ($F_{(1,179)}$=136.8; p<0.0001), treatment ($F_{(1,179)}$=14.35; p=0.0002), and interaction effect ($F_{(1,179)}$=25.11; p<0.0001). Sidak's multiple comparison showed that WT-GFP and WT -Foxp2 have a significantly greater difference in spine density compared to R6/1-GFP (p<0.0001 in both cases). Moreover, the R6/1-Foxp2 mice had also a significant greater spine density than R6/1-GFP (p<0.0001) indicating that thalamic Foxp2 overexpression significantly corrected dendritic spine density in the dorsal striatum of mutant treated mice (Figure 47A, B).

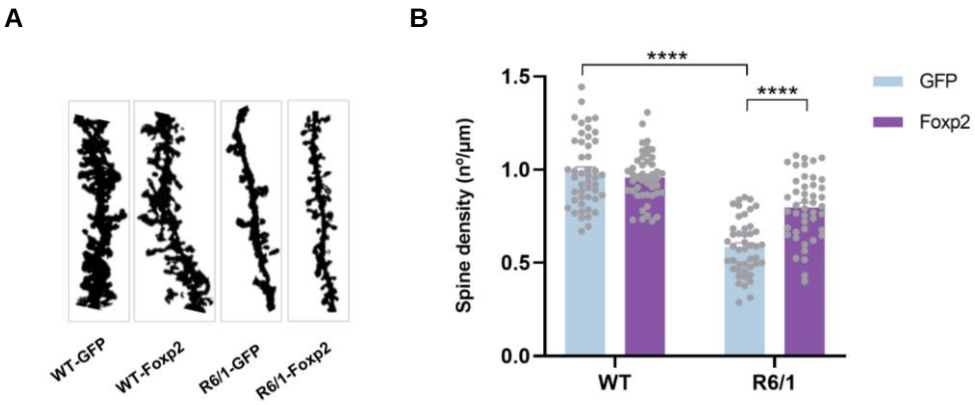


Figure 47. Spine dendritic analysis in the transduced symptomatic R6/1 mice striatum. (A) Representative photomicrographs showing striatal dendrites of WT-GFP, WT-Foxp2, R6/1-GFP and R6/1-Foxp2. **(B)** Histogram shows quantitative analysis of dendritic spine density per micrometer. Data were analyzed by two-way ANOVA test with genotype and treatment as factors. ****p < 0.0001. Sidak's post hoc test was performed. Data were expressed as (mean ± S.E.M) (~200 dendrites; n=3 animals per group).

6.7. Foxp2 thalamic overexpression corrects L4 somatosensorial cortical dendritic spine pathology in R6/1 mouse

To elucidate whether rescue of sensory deficits by Foxp2 overexpression in ventrolateral thalamus correlated with plasticity changes in the somatosensorial cortex (SS) -main afference of thalamus-, we next analyzed the dendritic spine density in Golgi-impregnated L4 stellae cortical neurons (barrel cortex neurons) in Foxp2 treated mice and control (Figure 48A). The dendritic spine density in stellae cortical neurons from R6/1 mice was reduced compared to WT, indicated by a genotype effect two-way ANOVA analysis ($F_{(1,82)}$=29.61; p<0.0001).

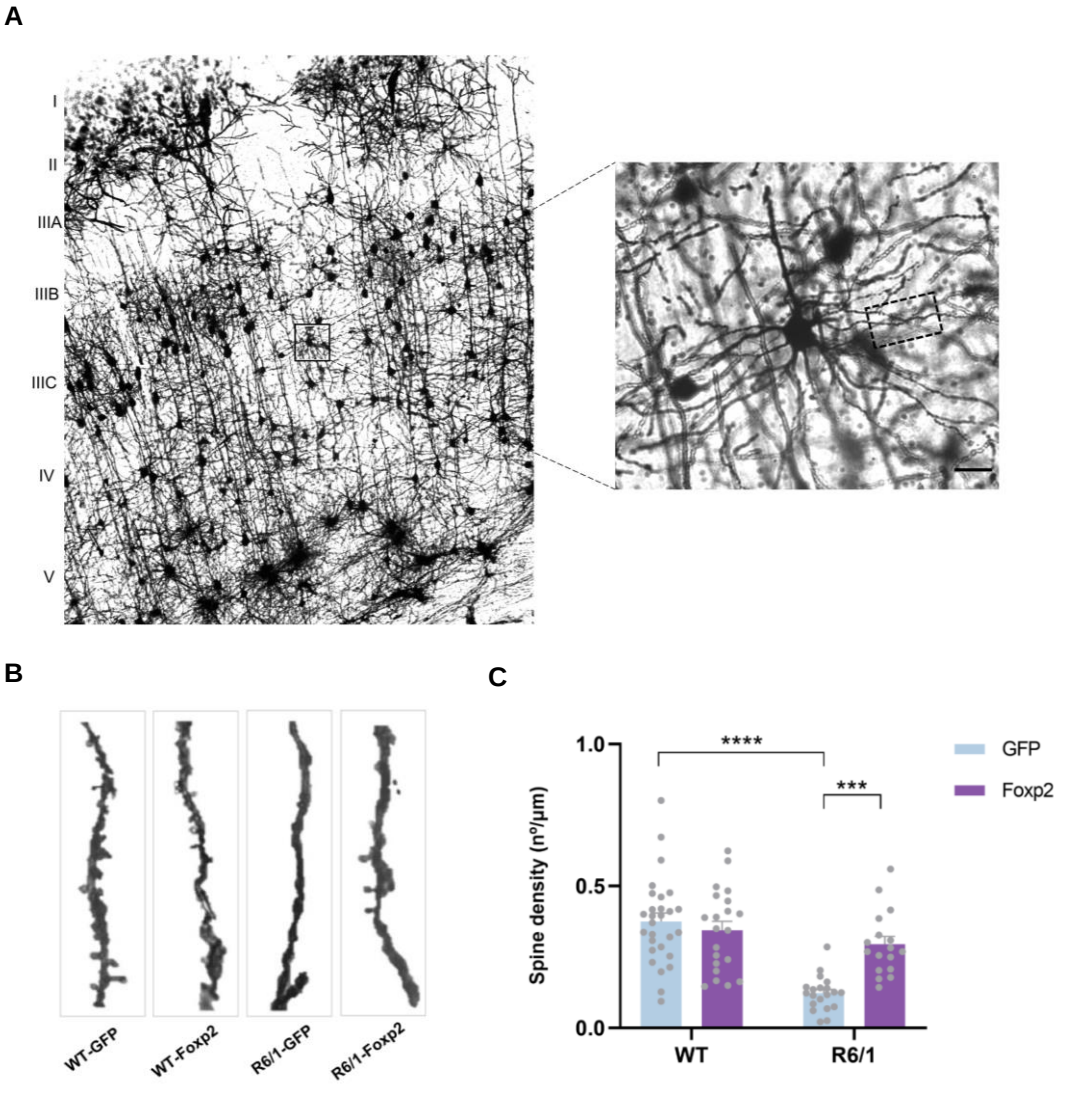


Figure 48. Spine dendritic analysis in the transduced symptomatic R6/1 mice L4 somatosensorial cortex (A) Representative photomicrograph of layers of somatosensorial cortex and L4 stellae cortical neuron. **(B)** Representative photomicrographs showing cortical dendrites of WT-GFP, WT-Foxp2, R6/1-GFP and R6/1-Foxp2. **(C)** Histogram shows quantitative analysis of dendritic spine density per micrometer. Data were analyzed by two-way ANOVA test with genotype and treatment as factors. ***p < 0.001, ****p < 0.0001.

Sidak's post hoc test was performed. Data were expressed as (mean ± S.E.M) (~100 dendrites; n=4-5 animals per genotype).

Two-way ANOVA also showed a treatment ($F_{(1,82)}$=6.496; p=0.0127), and interaction effect ($F_{(1,82)}$=13.49; p=0.0004). Tukey's post hoc analysis revealed that R6/1-GFP mice have a significant lower spine density compared to WT-GFP and WT-Foxp2 (p<0.0001 in both conditions) respectively. Further, R6/1-Foxp2 mice had also a significant greater spine density than R6/1-GFP (p=0.0005) indicating that thalamic Foxp2 overexpression significantly corrects somatosensorial dendritic spine pathology in R6/1 mouse (Figure 48B, C).

6.8. Thalamic Foxp2 overexpression fully restores ventrolateral thalamus degeneration in the R6/1 mouse

To determine the mechanism by which thalamic Foxp2 overexpression improved the behavioral performance of treated R6/1 mice, we analyzed the size of different key brain regions affected in HD (reviewed in Reiner et al., 2011). We aimed to elucidate whether thalamic Foxp2 overexpression could correlate with an increase in the size of those regions. As Foxp2 is a regulator of thalamic pattern (Ebisu et al., 2017), we first performed a cytochrome oxidase staining and then analyzed the volume of ventral posterior nucleus of the thalamus of Foxp2 overexpressed mice. The ventral posterior nucleus volume analysis showed the following means ± SEM for each experimental condition: WT-GFP = 2.016 mm3 ± 0.064 ; WT-Foxp2 = 1.982 mm3 ± 0.061 ; R6/1-GFP = 1.534 mm3 ± 0.115, and R6/1-Foxp2 = 1.956 mm3 ± 0.047.

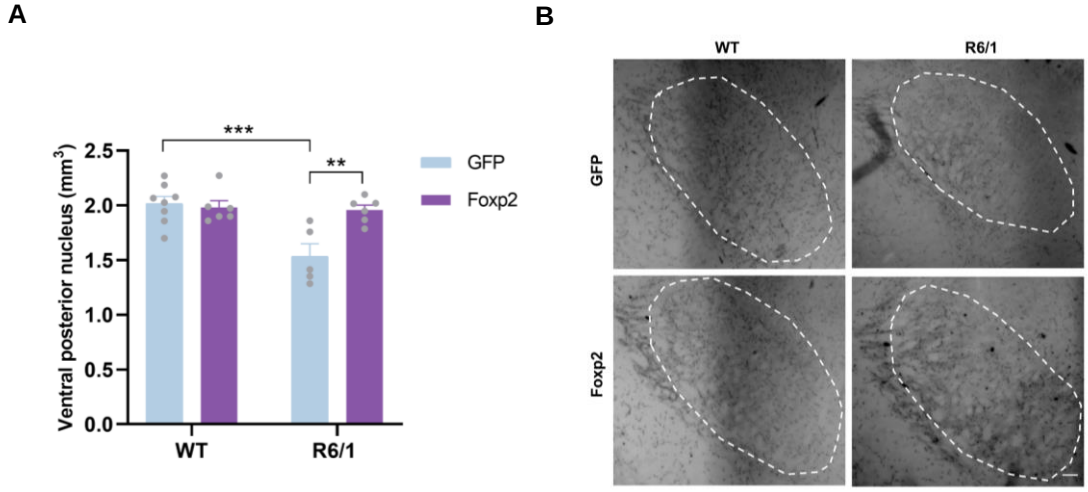


Figure 49. Evaluation of the ventral posterior nucleus volume in the thalamus transduced R6/1 mice. **(A)** Histogram shows quantitative analysis of the volume of ventral posterior nucleus in all experimental groups. **(B)** Representative photomicrographs of the volume of ventral posterior nucleus for each experimental condition. Data were analyzed by two-way ANOVA test with genotype and treatment as factors. **p < 0.01,

***p < 0.001. Tukey's post hoc test was performed. Data were expressed as (mean ± S.E.M) (n=5-8 animals per group).

The two-way ANOVA analysis indicated a significant genotype ($F_{(1,21)}$=9.812; p=0.0050), treatment ($F_{(1,21)}$=12.21; p=0.0022), and interaction effect ($F_{(1,21)}$=7.125; p=0.0144) (Figure 49A, B). Tukey's post hoc test was performed and showed that WT mice have a significant greater ventral posterior nucleus volume than R6/1-GFP (p=0.0006). Volume of R6/1-Foxp2 ventral posterior nucleus was significantly different from R6/1-GFP (p=0.0044). Moreover, R6/1-Foxp2 ventral posterior nucleus volume reached similar levels to WT mice ventral posterior nucleus volume, suggesting that Foxp2 overexpression fully delays ventrolateral thalamus neurodegeneration in R6/1 mice.

6.9. Partial rescue of striatal degeneration in R6/1 mice after thalamic Foxp2 overexpression

Next, we investigated the volume of the striatum of thalamic Foxp2 overexpressed mice, another main efferent of the thalamus. To this end, a Nissl staining was performed, and striatal sections were quantified. The striatal volume analysis showed the following means ± SEM for each experimental condition: WT-GFP = 10.050 mm3 ± 0.253 ; WT-Foxp2 = 10.200 mm3 ± 0.257 ; R6/1-GFP = 7.564 mm3 ± 0.173, and R6/1-Foxp2 = 8.418 mm3 ± 0.196. The two-way ANOVA analysis indicated a significant genotype ($F_{(1,44)}$=89.89; p<0.0001) and treatment effect ($F_{(1,44)}$=5.232; p=0.0270), but interaction effect was not observed ($F_{(1,44)}$=2.617; p=0.1129) (Figure 50A, B).

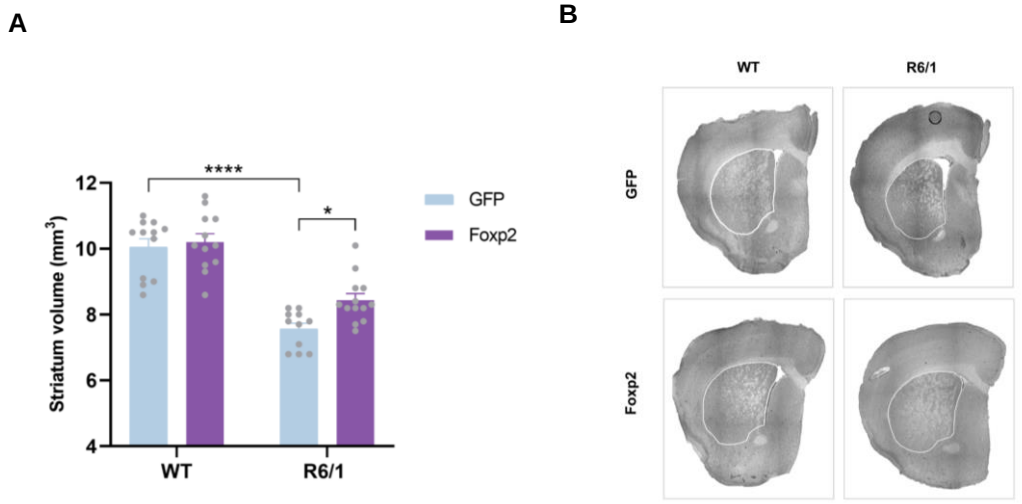


Figure 50. Evaluation of striatum volume in the thalamus transduced R6/1 mice. (A) Histogram shows quantitative analysis of striatum volume in all experimental groups. **(B)** Representative photomicrographs of striatum volume for each experimental condition. Data were analyzed by two-way ANOVA test with group and volume as factors. *p < 0.05, ****p < 0.0001. Data were expressed as (mean ± S.E.M) (n=12-13 animals per group).

Despite the lack of interaction, Tukey's multiple comparison test was performed and showed that WT mice have a significantly greater striatal volume than both R6/1-GFP mice ($p<0.0001$). Volume of R6/1-Foxp2 was significantly different from R6/1-GFP ($p=0.0407$), suggesting that Foxp2 overexpression slightly delayed striatal neurodegeneration in R6/1 mice.

6.10. Thalamic Foxp2 overexpression did not rescue the somatosensory cortex thickness loss in R6/1 mouse model

As Foxp2 recovery levels in ventrolateral thalamus showed a slightly delay in R6/1 striatum degeneration, we decided to investigate whether Foxp2 overexpression could exert an effect in thickness of somatosensory cortex. To address this question, we measured triplicates of the distance between the first and sixth cortical layer of the somatosensory cortex for each section of each animal and we then obtained the mean of the triplicates. Next, we compared the mean of the thickness of each section number across the 4 experimental conditions. Two-way ANOVA group effect indicated that somatosensory cortex thickness was significantly different between the 4 groups ($F_{(3,172)}=14.41$; $p<0.0001$). Somatosensory cortex thickness along the consecutive sections was also different ($F_{(6,172)}=138.7$; $p<0.0001$), but no interaction effect was seen ($F_{(18,172)}=0.5974$; $p=0.8982$) (Figure 51A,B). These results suggest that Foxp2 therapy was not efficient in the restoration of the somatosensory cortex thickness loss in the R6/1 mouse model.

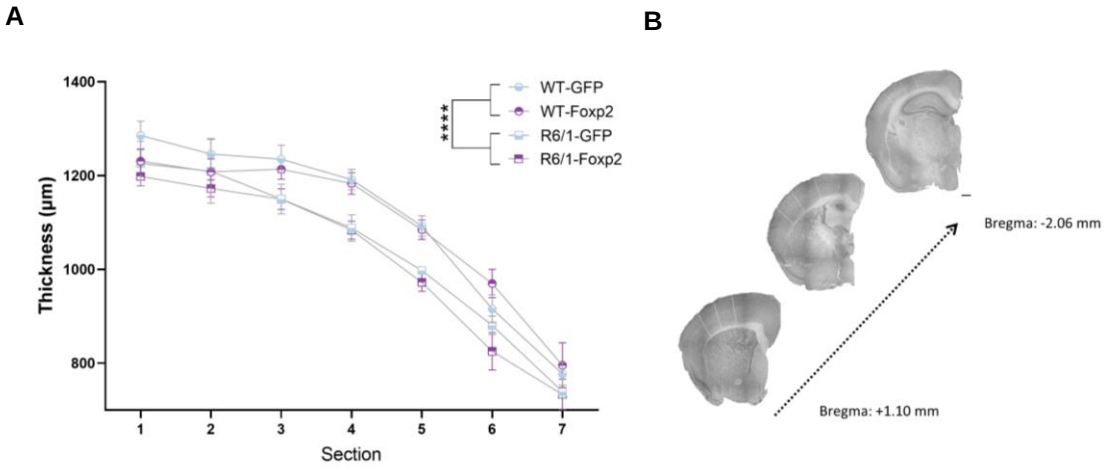


Figure 51. Evaluation of SS cortex thickness in the thalamus transduced R6/1 mice. (A) Histogram shows quantitative analysis of cortical thickness along coronal cortical section. **(B)** Representative photomicrographs showing progression of coronal sections starting from the first one -located +1.10 mm from Bregma- until the last one –located -2.06 mm from Bregma-. Data were analyzed by two-way ANOVA test with group and section as factors. ****$p < 0.0001$. Data were expressed as (mean ± S.E.M) (~210 coronal section; n=6-9 animals per group).

6.11. VGluT2-positive clusters are decreased at layer IV of the somatosensory barrel cortex, but not PSD-95-positive clusters

To investigate whether sensory deficits in the R6/1 mice were accompanied by decreased structural plasticity in the somatosensory cortex, and further examine the potential effects of Foxp2 overexpression in the ventrolateral thalamus, we next checked the excitatory postsynaptic sites in the barrel cortex of all experimental groups. To this end, an immunofluorescence against VGluT2 and PSD-95 was performed, and barrel cortex clusters were quantified (Figure 52A, B). Regarding VGluT2-positive clusters, two-way ANOVA analysis indicated a significant genotype ($F_{(1,22)}$=10.25; p=0.0041) and interaction effect ($F_{(1,22)}$=5.805; p=0.0248), but treatment effect was not observed ($F_{(1,22)}$=0.02101; p=0.1129) (Figure 52C, D).

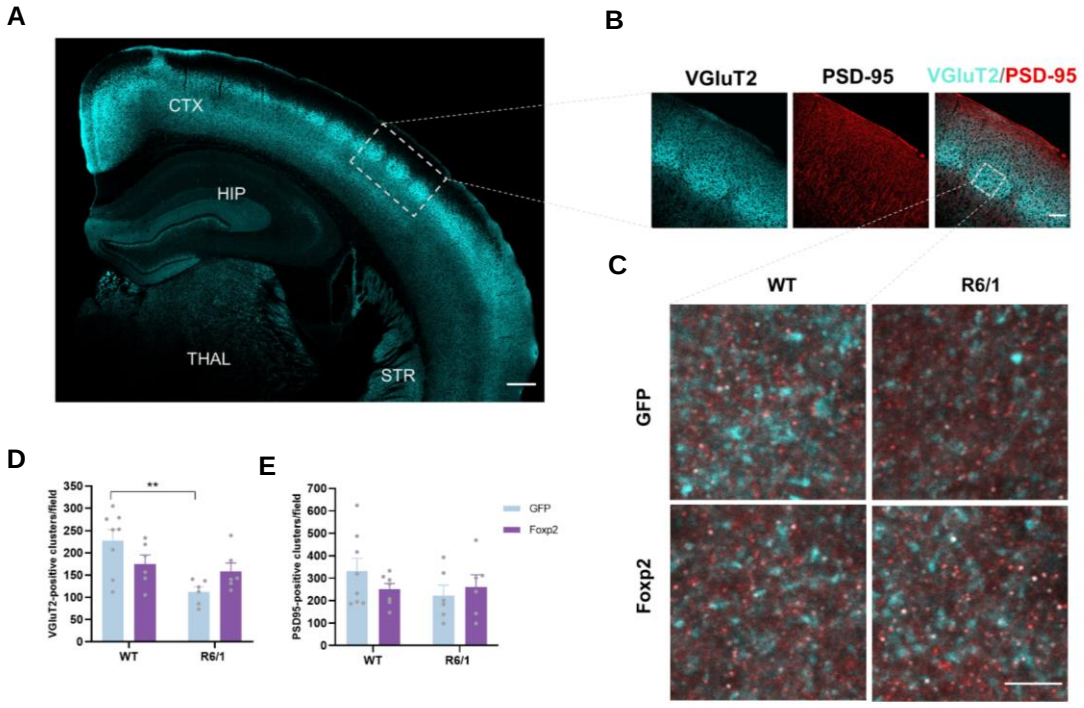


Figure 52. Evaluation of synaptic marker in the somatosensory cortex in the thalamus transduced R6/1 mice. (A) Representative photomicrograph of VGluT2-staining in the barrel cortex of a WT mouse. Scale bar: 300µm. **(B)** Representative photomicrographs (high magnification) showing double labelling of VGluT2- and PSD-95-positive clusters in a WT mouse. Scale bar: 100µm. **(C)** Representative photomicrographs (high magnification) showing double labelling of VGluT2- and PSD-95-positive clusters of WT-GFP, R6/1-GFP, WT-Foxp2 and R6/1-Foxp2. Scale bar: 5µm. **(D)** Histogram shows quantification of the average of VGluT2-positive clusters in the barrel cortex. **(E)** Histogram shows quantification of the average of VGluT2-positive clusters in the barrel cortex. Data were analyzed by two-way ANOVA test with genotype and treatment as factors. **p < 0.01. Data were expressed as (mean ± S.E.M) (n=6-9 animals per group).

Tukey's multiple comparison test was performed and showed that VGluT2-positive clusters/field in WT-GFP mice was significantly greater than R6/1-GFP ($p=0.0024$), but not significantly different when compared with R6/1-Foxp2 ($p=0.1866$). Regarding PSD-95-positive clusters, two-way ANOVA analysis indicated neither genotype ($F_{(1,23)}=1.004$; $p=0.3269$) nor interaction ($F_{(1,23)=}1.458$; $p=0.2394$), nor treatment effect ($F_{(1,23)}=0.1906$; $p=0.6665$) (Figure 52C, E). Altogether, these data suggest that presynaptic excitatory sites in the barrel cortex, rather than postsynaptic sites, are disrupted in the symptomatic R6/1 mice. In addition, thalamic Foxp2 overexpression could regulate these disturbances.

7. Downregulating Foxp2 levels in ventrolateral thalamus mimics HD motor-sensory alterations

To test whether lowering of Foxp2 levels could lead to HD motor-sensory disturbances, we next transduced ventrolateral thalamus of 10-11-week-old WT mice with an AAV8-short hairpin RNA (shRNA) construct targeting Foxp2 under a U6 promoter. Control group was injected with an AAV8 expressing only mCherry. We waited for 4 weeks until the virus expression was stable and then subjected the animal to an array of behavioral test (Figure 53A, B).

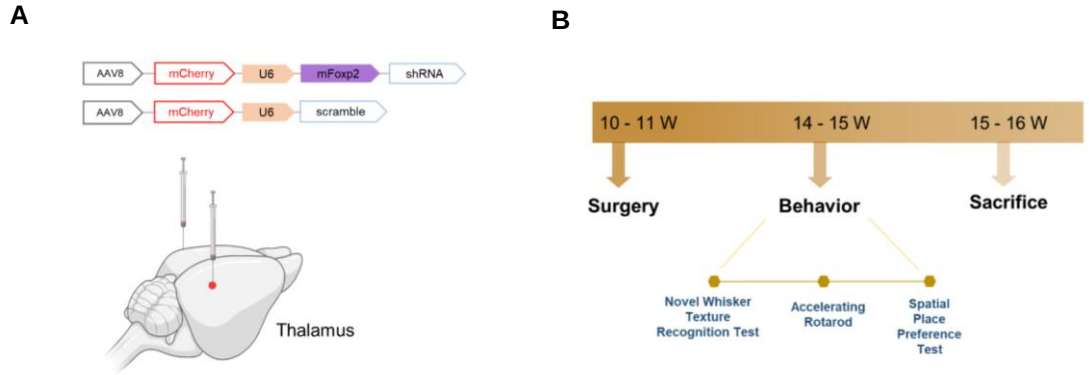


Figure 53. Experimental Design of Foxp2 Thalamus Downregulation. (A) Viral constructs injected in the ventrolateral thalamus of WT mice. **(B)** Timeline.

7.1. Verification of Foxp2-Downregulation in the thalamus of WT mice

To confirm the downregulation of Foxp2 levels in the thalamus of adult WT-shFoxp2 mice and WT-scramble controls we performed a western blot against Foxp2. Interestingly, western blot analysis revealed that Foxp2 levels expression were significantly decreased in WT-shFoxp2 thalamus when compared with WT-scramble controls (Figure 54).

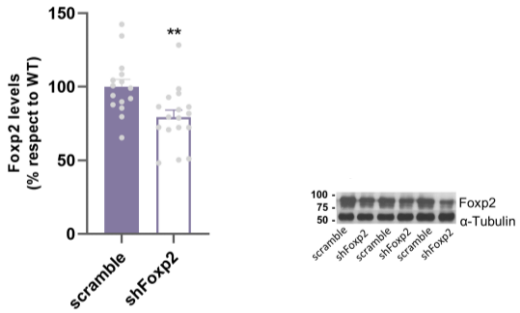


Figure 54. Expression of Foxp2 in the thalamus of WT-shFoxp2. Densitometric analysis showing protein levels of Foxp2 in WT-shFoxp2 and WT-scramble. Protein levels were normalized with tubulin as loading control. Representative immunoblots are shown below. Data were analyzed by Student's two-tailed t test. **$p < 0.01$. Data were expressed as (mean ± S.E.M) (n= 15-17 animals per genotype).

7.2. Downregulating Foxp2 levels in ventrolateral thalamus mimics HD whisker-sensory disturbances

Both groups, WT-scramble and WT-shFoxp2 mice were subjected to a battery of motor-sensory test (Figure 55A). Novel whisker-dependent texture discrimination test was conducted as described elsewhere (Wu et al., 2013) (Figure 55B). We first measured locomotor and exploratory activity during 2 days of habituation in the open field. Only data from day 1 of habituation (Figure 55C) is shown as representative of the following parameters: distance, mean speed and time in the center. All experimental groups traveled similar distances (Figure 55D) at similar speed ratio (Figure 55E). Also, all experimental groups spent similar times in the center of the open field, suggesting similar levels of anxiety (Figure 55F).

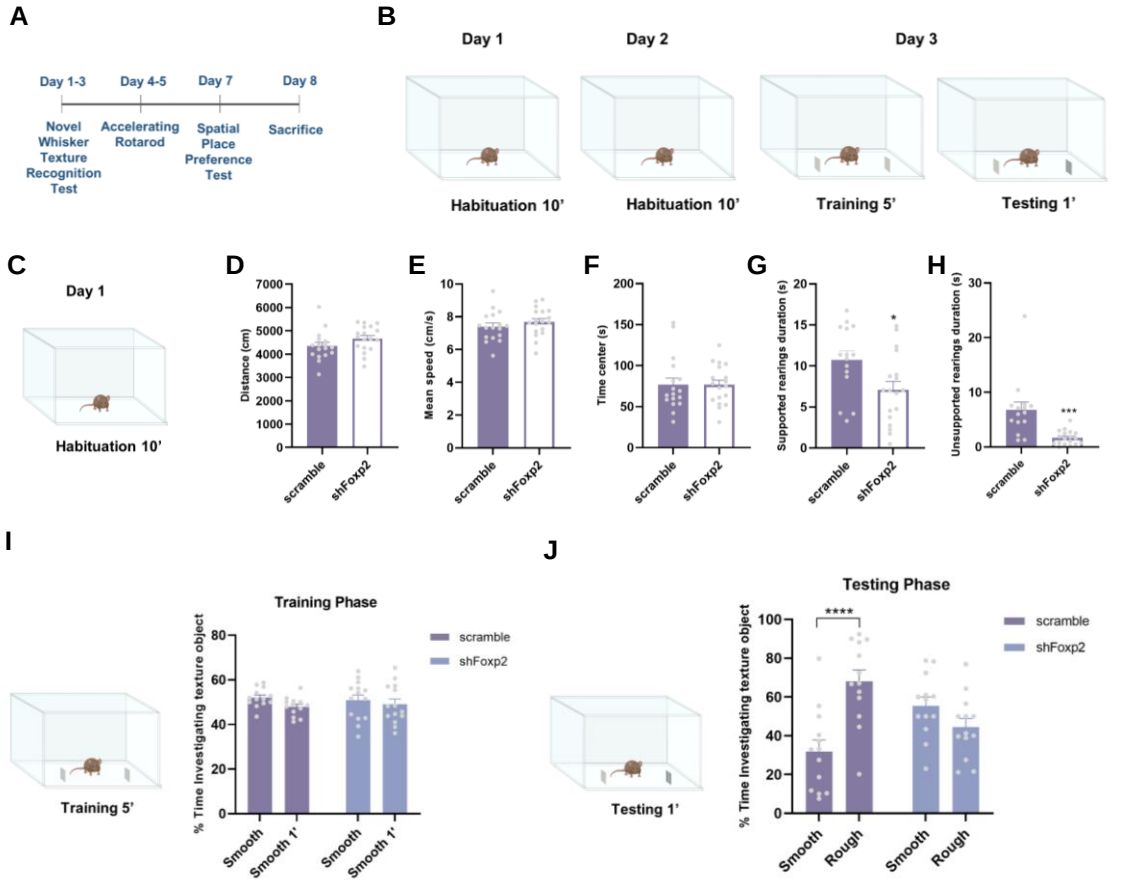


Figure 55. WT-shFoxp2 and WT-scramble mice performance in a barrel cortex-dependent sensory-discrimination learning task. (A) Battery of sensory-motor behavioral test. **(B)** Novel Whisker Texture Discrimination Task (NWTDT**). (C)** Day 1 of habituation in the open field. **(D)** Distance. **(E)** Mean speed. **(F)** Time in the center. **(G)** Supported rearing. **(H)** Unsupported rearing. **(I)** % Time investigating texture object during training phase. **(J)** % Time investigating texture object during testing phase. Data were analyzed by Student's two-tailed t test. *$p < 0.05$, ***$p < 0.001$ and two-way ANOVA with object and group as factors. Bonferroni's post hoc test was performed. ****$p < 0.0001$. Data were expressed (as mean ± S.E.M) (n=13-17 animals per group).

Similarly, only data from day 1 of habituation is shown as representative of the following parameters: supported rearing (exploratory behavior) and unsupported (emotional-like behavior) (Sturman et al., 2018), indicating the levels of exploratory activity. Interestingly, WT-shFoxp2 spent less time in supported rearing ($t_{(31)}$=2.432; p=0.02) and unsupported rearing ($t_{(31)}$=3.950; p=0.0004) than WT-scramble (Figure 55G, H). On the third testing day, during training phase, both groups explored the two similar smooth-textured objects in the arena, without preference (Figure 55I). Surprisingly, during the testing phase, WT-shFoxp2 showed an impairment in sensory-whisker discrimination as described by two-way ANOVA with significant object effect ($F_{(1, 48)}$=5.734; p=0.0206) and interaction effect ($F_{(1,48)}$=20.3; p<0.0001), even when no group effect was seen ($F_{(1,48)}$=4.384e-019); p>0.9999). Bonferroni's pos hoc analyses yielded up that WT-scramble (p<0.0001) could discriminate between the familiar smooth texture and the novel rough texture, but not WT-shFoxp2 (p=0.2826) (Figure 55J). Overall, these data indicated that single Foxp2 knockdown in the ventrolateral thalamus was fully able to replicate HD exploratory deficits and whisker-sensory disturbances.

7.3. Lowering Foxp2 levels in ventrolateral thalamus mimics HD motor deficits

We next assess motor learning and coordination, WT-scramble and WT-shFoxp2 were subjected to an accelerated rotarod test, and latency to fall was measured.

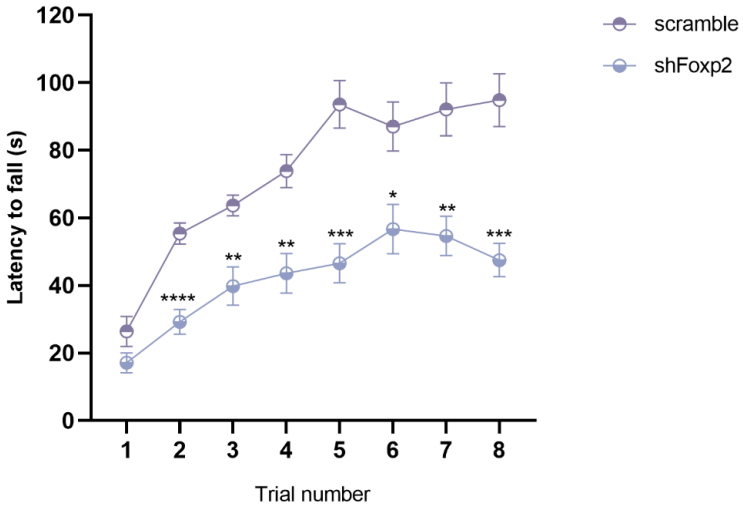


Figure 56. Motor performance of WT-shFoxp2 and WT-scramble mice. (A) Latency to fall in the accelerating rotarod task. Data were analyzed by repeated measures ANOVA with group and time as factors. Bonferroni's post hoc test was performed.*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Data were expressed as (mean ± S.E.M.) (n=17-18 animals per group).

Interestingly, latency to fall from the rod was decreased in WT-shFoxp2 respect to WT-scramble. Repeated measures ANOVA showed a significant group effect ($F_{(1,31)}$=28.16; p<0.0001), time ($F_{(4.712,146.1)}$= 39.49, p<0.0001), and interaction ($F_{(7,217)}$=4.678; p<0.0001) (Figure 56). These data suggested that single Foxp2 knockdown in the ventrolateral thalamus was fully able to replicate HD motor deficits.

7.4. Silencing Foxp2 levels in ventrolateral thalamus does not induce tactile sensory alterations

We next evaluated the time animals spent on a preferred tactile texture as a measure of tactile sensory perception (Figure 57A). Both groups, WT-scramble and WT-shFoxp2 spent similar times in the smooth and rough textures indicated by two-way ANOVA with texture effect ($F_{(1,64)}$=9.319; p<0.0001), but neither group ($F_{(1,64)}$=0.09591, p=0.7578), nor interaction effect ($F_{(1,64)}$=0.1044; p=0.7477) were observed (Figure 57B, C). These data suggested that both WT-scramble and WT-shFoxp2 have similar tactile preference sensory perception, and Foxp2 knockdown in the ventrolateral thalamus was not able to induce tactile sensory alterations.

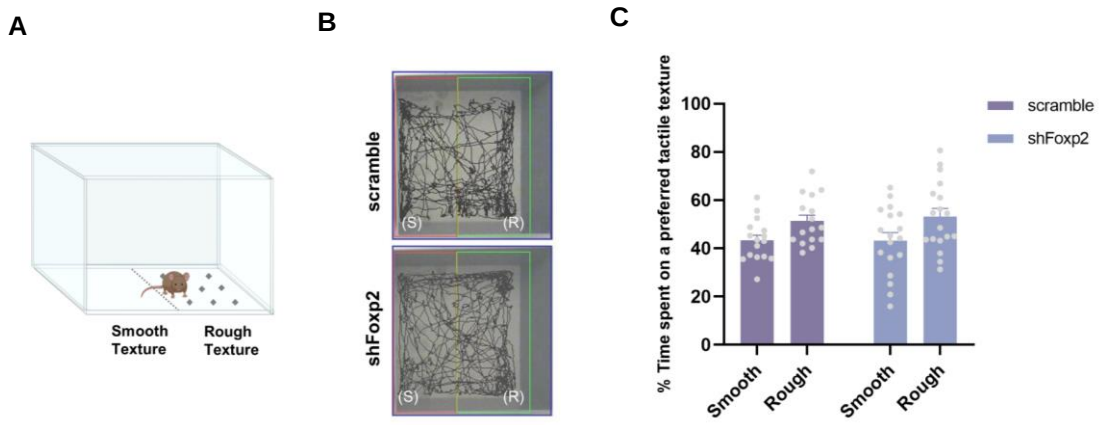


Figure 57. Assessment of tactile sensory perception in WT-shFoxp2 and WT-scramble mice. (A) Spontaneous preference place test. **(B)** Representative images of path mice in the arena. **(C)** % Time spent on a preferred tactile texture. Data were analyzed by repeated measures ANOVA with group and texture as factors. Data were expressed as (mean ± S.E.M.) (n=14-18 animals per group).

DISCUSSION

HD is a disabling condition involving a cascade of neurodegenerative processes which eventually lead the HD mutation carriers to death, in a period of a few decades. Scientific efforts had failed in the pursue of a current cure, since available treatments are uniquely oriented to alleviate motor, and psychiatric disease symptoms, to a lesser extent. Paradoxically, several studies consistently reported that psychiatric disturbances worsen quality of life to a greater extent than motor symptoms of the disease (Helder et al., 2001; Ho et al., 2009; Ready et al., 2008). Moreover, tetrabenazine the only drug approved in the treatment of hyperkinetic movements (Marshall, 2006; Paleacu et al., 2004) can be found to be discontinued by patients mainly due to a lack of treatment effectiveness and/or worsening of psychiatric disturbances as depression (Claassen et al., 2018).

Along the past decades, HD clinical and biomolecular landscape has become clearer and more reachable. Multicomplex arrays including histobiochemical analysis of HD postmortem brains, *in vivo* multimodal MRI and PET studies have provided evidence of major neurobiochemical, neuropathological and metabolic changes in HD patients (Albin et al., 1991; Augood et al., 1996; Feigin et al., 2007; Koroshetz et al., 1997; van Oostrom et al., 2007; Schippling et al., 2009; Taylor-Robinson et al., 1996). Also, cellular and animal murine models have revealed prior cellular and molecular pathogenic events triggered by mHtt before neurodegeneration and death of neuronal populations (Bates et al., 2015; Zuccato et al., 2010; Jiang et al., 2016; Jimenez-Sanchez et al., 2017; Ross & Tabrizi, 2011). From these studies, it can be deduced that a synergy between deleterious effects of mHtt and complex compensatory mechanisms occur during the disease, starting with the synaptic and neuronal dysfunction until the inexorable death of the striatal neurons and development of the clinical symptoms. As mentioned above, early hyperkinetic-stage and dystonic late-stage symptoms of HD emerge from prominent alterations in DA transmission (Garrett & Soares-da-Silva, 1992; Kish et al., 1987). Additionally, some psychiatric disturbances which can precede the classical motor symptoms by up to a decade (Epping et al., 2016) are potentially caused by the fronto-striatal dysfunction in HD (Anderson & Marder, 2001; Goh et al., 2018), whereas sleep alterations have been associated with hypothalamic dysfunction and disruption of circadian rhythmicity in HD (Petersén, 2006). Moreover, an enhanced thalamic activation in preclinical HD subjects during the performance of a motor learning task (Feigin et al., 2006, 2007) emerges as a compensatory mechanism of cortico-striatal dysfunction. Interestingly, prior to these functional alterations, several cellular processes are progressively compromised by mHtt in an indiscernible way, resulting in disturbances in synaptic plasticity and neurotransmission and homeostatic dysregulation. Eventually the impairment and

disintegration of the entire HD network becomes evident through the behavioral and functional disabilities. Hence, we found particularly necessary to sought and decipher the initial key mechanism of the disease in prodromal stages and design useful therapeutic strategies able to delay the onset and the neuropathologic changes and clinical symptoms in HD.

In this thesis we have analyzed the early dysregulation of a candidate gene named Foxp2 which seems to be linked to early behavioral and molecular changes in the juvenile R6/1 mouse model. Juvenile R6/1 mice behavioral phenotype was characterized by increased hyperlocomotive and impulsive-like behavior, less aggressive-like behavior and disrupted locomotor circadian rhythms converging with structural and functional changes as decreased dendritic spine density and dysregulation of striatal gene expression. Interestingly, the rescue of striatal Foxp2 levels reverted impulsivity-phenotype, delayed the striatal dendritic pathology and restored striatal protein dysregulation. Dysregulation of Foxp2 in the thalamus of pre- and symptomatic R6/1 mouse was also described. Also, we confirmed the well-established cortico-striatal disconection previously seen in HD models, but also demonstrated the functional disconnection between thalamus and striatum at symptomatic stages of R6/1 mice. Recovery of Foxp2 in the ventrolateral thalamus rescued sensory and motor deficits in the R6/1 mice, along with structural and functional changes, whereas knockdown of Foxp2 in wild type mice mimicked HD-associated phenotype.

1. Deciphering the role of Foxp2 in early behavioral deficits and striatal vulnerability in HD

Transcriptional dysregulation is a central pathogenic mechanism in HD that is faithfully recapitulated in mouse models. The presence of mHtt compromising transcriptional profiles of several genes have been detected in both, HD patients and animal models (Augood et al., 1996, 1997; Cha et al., 1998). Importantly, transcription factors have been a major target for mHtt, since an enhanced or decreased interaction resulted in a detrimental effect by diminishing or cancelling its regular roles such neuroprotection, anti-apoptotic function, or gene transcriptional regulation (Gao et al., 2019; Hernández et al., 2017; Steffan et al., 2000; Yildirim et al., 2019; Zuccato et al., 2007). Conversely, the rescue of these transcription factors and/or their putative target genes has been enough proof of its beneficial effects including the attenuation of polyglutamine-induced apoptosis and the mHtt-mediated toxicity or the restoration of aberrant neuronal gene transcription (Hernández et al., 2017; Yildirim et al., 2019; Zuccato et al., 2007). Recently, it has been described that Foxp2, a

member of the Fox transcription factor family, interacts with mHtt resulting in the reduction of its expression. In fact, Foxp2 levels have been found decreased in the striatum of HD patients and HD models. Interestingly, reduced levels of Foxp2 might contribute to the appearance of motor phenotypes associated with HD (Louis et al., 2017; Hachigian et al., 2017), while overexpression of Foxp2 can alleviate these phenotypes, likely by restoring synaptic function (Hachigian et al., 2017). In despite of these relevant results, the role of Foxp2 in HD has been poorly addressed and only in very advanced stages of the disease. In this thesis, we hypothesized that transcriptional dysregulation of Foxp2 could occur at early stages of the disease and in several brain regions, contributing to the onset and progression of basal ganglia circuitry dysfunction and associated synaptic alterations. As we theorized, our outcomes revealed an early downregulation of Foxp2 striatal levels in the R6/1 mice at PND15, which was consistently maintained in the consecutives 4, 8, 12 and 20-week-old. As we previously referred, mHtt through the polyQs fragments aggregates into insoluble forms sequestering essential proteins, such as transcription factors (Nucifora et al., 2001; Steffan et al., 2000, 2001). Distinguishing presence of mHtt aggregates in the R6/1 mouse striatum was first described at 8-week-old, whereas at 3-week-old it was an absence of intracellular inclusions (Hansson et al., 2001). Nevertheless, we aimed to dismiss the possibility that reduction of Foxp2 levels could result from a mHtt-dependent sequestration of Foxp2 inside the intracellular inclusions. Interestingly, we found nuclear diffuse staining and distinctly round immunolabeled nuclear inclusions in the striatum of juvenile R6/1 mouse. Also, Foxp2 staining showed a partial co-aggregation with mHtt. From this result, we deduced that Foxp2 dysregulation might arise in part from a potential interaction with mHtt. Nonetheless, a partial colocalization of Foxp2 with mHtt cannot explain entirely the substantial reduction of striatal Foxp2 at the early PND15. In fact, the view of a transcriptional dysregulation mainly caused by mHtt sequestration has been challenged since some studies have described disruption of transcriptional profiles prior to inclusions formation, while others have documented a lack of colocalization between Htt aggregates and polyglutamine-containing transcription factor in HD mice, suggesting that altered gene expression probably results from the interaction between nuclear transcription factors and soluble mHtt, rather than sequestration by nuclear inclusions (Dunah et al., 2002; Yu et al., 2002). In our research, a future study could include an assessment of Foxp2 mRNA levels which could bring some insights about the potential mechanism underlying early Foxp2 dysregulation.

Although Foxp2 was first described in relation with speech and language deficits, subsequent investigations have consistently postulated FOXP2 gene as a relevant risk factor for

schizophrenia (Tolosa et al., 2010; T. Li et al., 2013; X. Li et al., 2009; Liégeois et al., 2003; Rao et al., 2017; Sanjuán et al., 2006; Španiel et al., 2011). FOXP2 has been linked with other psychiatric features such as ADHD, risk-taking behavior, insomnia, and major depression (Clifton et al., 2018; Demontis et al., 2019; Lane et al., 2017; T. Li et al., 2013; Soler Artigas et al., 2019). Also, some of its putative neuronal targets have been associated with a range of brain-related phenotypes, including autism, schizophrenia, bipolar disorder, and depression (Brandon et al., 2009; Burdick et al., 2010; Friedman et al., 2007; Ji et al., 2013; St Clair et al., 1990). Accordingly, *FOXP2* gene begins to be considered as a potential susceptibility locus in neuropsychiatric disorders (Khanzada et al., 2017). Interestingly, some of these psychiatric features related with *FOXP2* common variations resemble to those observed in HD patients, suggesting that *FOXP2* changes could underlie psychiatric symptoms in HD. As previously reviewed, HD mutation carriers can develop personality changes including apathy, depression, anxiety, psychosis, insomnia, irritability, impulsivity, and risk-taking behavior among others (Anderson & Marder, 2001; Goh et al., 2018). Although investigations have been mainly focused on motor symptoms, several studies emphasize that those psychiatric disturbances worsen quality of life to a greater extent than the motor symptoms of the disease (Helder et al., 2001; Ho et al., 2009; Ready et al., 2008), and have been shown to exert a greater impact on levels of functional disability in early stages of the disease (Hamilton et al., 2003). Importantly, HD murine models have faithfully reproduced some of the psychiatric disturbances manifested by HD patients, including an anxiety- and depressive-like phenotype (Brito et al., 2019; C.-T. Chiu et al., 2011; Ciamei & Morton, 2008; Grote et al., 2005; Hickey et al., 2005; L. Menalled et al., 2009; Orvoen et al., 2012; Pouladi et al., 2009; Renoir et al., 2011), along with abnormal social interaction (Shelbourne et al., 1999; Wood & Morton, 2015) and disruption of circadian rhythms (Kantor et al., 2013; Loh et al., 2013). However, behavioral studies have been mostly oriented to the study of psychiatry alterations in middle-late stages of the disease, while the assessment of psychiatric spectrum in early stages has been poorly addressed.

As we hypothesized, our data suggested that Foxp2 transcriptional dysregulation with concomitant presence of mHtt aggregates at 4-week-old mice correlated with an early behavioral phenotype displayed by the juvenile R6/1 mice, characterized by increased hyperlocomotive and impulsive-like behavior, less aggressive-like behavior, and disrupted locomotor circadian rhythms, without any sign of anxiety- or depressive-like behavior. Interestingly, our results supported a previous postnatal behavioral phenotype reported in two HD murine models. In this study, the HD mice displayed a decreased anxiety, increased

risk-taking behavior, and reduced emotionality at postnatal stages (Siebzehnrübl et al., 2018). Remarkably, our findings successfully recapitulated the HD clinical scenario, in which the appearance of the main psychiatric alterations occurs prior to the first motor abnormalities, and it seems to be caused by the fronto-striatal dysfunction (Epping et al., 2016; Goh et al., 2018; Thompson et al., 2012). We showed that psychiatric-like manifestations displayed by R6/1 mice occur several weeks before any sign of motor impairment. Moreover, hyperlocomotion, impulsiveness and less-aggression exhibited by juvenile R6/1 mice, have been shown to be regulated by cortico-basal ganglia circuit (particularly on dopaminergic neurotransmission in the NAcc) (Dalley & Robbins, 2017; King et al., 2003; Lischinsky & Lin, 2020; Patil & Brid, 2010; Rouillon et al., 2007; Taepavarapruk et al., 2000), whereas locomotor circadian rhythms are partially regulated by the dorsal striatum (Miyazaki et al., 2021). We confirmed R6/1 mice hyperactivity in the open field at 4-week-old, which has been previously described elsewhere (Bolivar et al., 2004), and described similar control deficits to those reported in the R6/2 mouse model, and in the tgHD rat model (Balci et al., 2009; Massioui et al., 2016).

Interestingly, we showed a disruption of locomotor circadian rhythms in the juvenile R6/1 mice, which exhibited an enhanced locomotor activity during the nocturnal phase. In the same line, other studies have demonstrated a decline in circadian rhythms of activity and sleep in HD mouse models at late stages, showing a progressive age-dependent reduction of the wakefulness or levels activity during the dark phase (Kantor et al., 2013; Loh et al., 2013). Altogether, these results consolidate the view of a symptomatic progression in HD, characterized by an early hyperactivation of circuits and behavioral outputs which eventually lead to hypoactivation (Bolivar et al., 2004; Cepeda et al., 2003; Feigin et al., 2006, 2007; Garrett & Soares-da-Silva, 1992; Kish et al., 1987; Paulsen et al., 2004; Saft et al., 2008). Worth mentioning that aggressive dimension diverges between HD patients and mouse models, when the last ones are subjected to a resident-intruder paradigm. Although full-length models displayed significantly shorter latency and more aggressive behavior towards the intruder, R6/2 mice showed a lack of interest for the intruder at late stages of the disease compared to WT mice (Shelbourne et al., 1999; Wood & Morton, 2015). In our study, an aggressive-like phenotype was also missing in the juvenile R6/1 mouse model indicating that these alterations have a very early onset.

Even when the behavioral manifestations described in this thesis are associated with the cortico-striatal pathway (Dalley & Robbins, 2017; King et al., 2003; Lischinsky & Lin, 2020; Patil & Brid, 2010; Rouillon et al., 2007; Taepavarapruk et al., 2000), some of them are

canonically regulated by brain regions of the limbic system such amygdala or hypothalamus (Kerr et al., 2015; D. Lin et al., 2011; Siegel et al., 1999; Steele et al., 2021). Nevertheless, behavioral aggressive deficits have been reported in the absence of limbic regions malfunction, and rather associated with major glutamatergic deficiency and elevated dopamine in striatum (Adamczyk et al., 2012). In fact, the role of dopamine in striatum and NAcc regarding the formation of aggressive and impulsive traits has been increasingly accepted and standardized (Hahn et al., 2011; Tiihonen et al., 1995). Additionally, abnormalities in volume and activity levels in basal ganglia has been extensively reported in relation with these behavioral alterations (Amen et al., 1996; Soderstrom et al., 2002). Rhythmic processes are coordinated by the master circadian clock located in the suprachiasmatic nucleus (SCN) (Ralph et al., 1990; Schwartz & Zimmerman, 1991), although locomotor circadian rhythms can be partially regulated by the dorsal striatum (Miyazaki et al., 2021). In fact, age-dependent circadian disruption in the behavior of the zQ175 HD model has been described in association with dysregulated activity of the SCN or without any evidence of loss of cells or disruption of the central circadian pacemaker (Loh et al., 2013; Smarr et al., 2019).

In an effort to evaluate the extent of Foxp2 dysregulation, we analyzed Foxp2 levels in the cortex and NAcc of the R6/1 mice, knowing that both brain regions constitute a well-known neural substrates underlying the observed behavioral deficits. Surprisingly, the levels of Foxp2 in the cortex of R6/1 mice were decreased from 8 weeks of age, and Foxp2 levels in the NAcc showed a tendency towards decrease but were not significantly altered at 4 weeks of age, suggesting that early psychiatric manifestations in the R6/1 mice occurs in the absence of Foxp2 alterations in these brain regions. The specific region-dependent reduction of Foxp2 affecting the dorsal striatum at so early stages reinforces the notion of the striatal vulnerability in HD and suggest that the behavioral phenotype displayed by juvenile R6/1 mouse predominantly correlates with the reduction of Foxp2 in the dorsal striatum, rather than the changes in the cortex, or the NAcc. Although among subcortical regions NAcc has been traditionally associated with the behavioral responses described in this thesis, *in vivo* MRI analyses in humans in conjunction with pharmacological and experimental lesion studies in animal models have shown the solely involvement of the dorsal striatum along with changes in biochemical correlates in regarding of hyperlocomotion, choise-impulsivity task and aggression (Glenn & Yang, 2012; Kim & Im, 2019; Koshikawa et al., 1989; Tedford et al., 2015). Additionally, genetic manipulations of Foxp2 in mice have been associated with altered social behaviors (Herrero et al., 2021; Medvedeva et al., 2019), and increased

locomotor and exploratory activity along with enhanced dopamine levels in subcortical regions such striatum and NAcc (Enard et al., 2009). Moreover, alterations in the levels of Cntnap2, a major target gene of Foxp2, induces locomotor hyperactivity in the open field and altered locomotor circadian rhythms (Adam et al., 2017; Scott et al., 2019).

In the Foxp2 overexpression experiments, impulsivity levels of juvenile R6/1 mice were entirely restored reaching similar levels compared to WT mice controls. Disadvantageously, the relationship between Foxp2 and impulsivity has been poorly addressed in animal studies, on the contrary GWAS analyses in humans have extensively established the implication of Foxp2 locus with ADHD, and the associated *impulsivity* dimension (Dark et al., 2018; Demontis et al., 2019; Faraone & Larsson, 2018; Ribasés et al., 2012). Altogether, this result suggested that impulsive phenotype is highly dependent on striatal Foxp2 regulation in the R6/1 mice. Impulsivity phenotype has been positively correlated with the initiation of substances use, or with maladaptive clinical addictions (Belin et al., 2008; Jentsch et al., 2014; Quinn et al., 2011). Pathological gambling behavior, adverse social behavior and reckless driving among other risk-taking behavior have been largely documented in HD patients (Jensen et al., 1998; Jhanjee et al., 2011; McDonell et al., 2020; Rebok et al., 1995; Schultz et al., 2017). Interestingly, during a perfomance in the Cambridge Gambling Task (CGT), which evaluates decision-making and impulsive behavior, prodromal HD patients shows impulse control deficits in the absence of risk-taking or poor judgment. In the light of these findings, the researchers postulated that gambling behavior relies more in a predisposition to impulsivity, rather than a genuine risk-taking behavior (Galvez et al., 2017), as has been suggested in other studies (Rogers et al., 1999a; Rogers et al., 1999b). Intriguingly, we found these insights closely related to our findings, since we corroborated the impulsive phenotype exhibits by juvenile R6/1 mouse in the jumping test, without any sign of anxiety- or risk-taking behavior, which can be assessed in the open field or the elevated plus maze. Dopamine has been traditionally related to impulsivity (Congdon & Canli, 2005). Pharmacological enhancement of dopamine activity increases impulsivity in humans, while administration of dopaminergic antagonists reduces impulsive responding in patients and control subjects (Aron et al., 2003; Pine et al., 2010). Additionally, dopamine D2 receptor has been implicated in the pathophysiology of various psychiatric disorders, including impulse control conditions and addiction-related behaviors (Janssen et al., 2015; Linden et al., 2018). Moreover, higher dopamine receptor D1 mRNA levels receptor in the prefrontal cortex and NAcc may predict greater impulsive action (Simon et al., 2013), while the discovery of dopamine receptor D1 polymorphisms in humans support a role of dopamine receptors D1 in impulsive behaviors

(Moses et al., 2019). Looking for potential mechanisms that could explain how Foxp2 could regulates impulsive-like behavior in the R6/1 mice, we found that disruptions of FoxP2 expression in at least two behavioral studies result in reduced expression of D1 receptor whereas D2 receptor expression was spared (Co et al., 2019; Xiao et al., 2021). Interestingly, a deficient Foxp2 mice showed increased impulsive-like behavior and concurrent increase in dopamine content in the rostral striatum and medial prefrontal cortex (Jhang et al., 2017), suggesting that increased dopamine neurotransmission might underlies impulsiveness in mice. In our work, whether dopamine receptor or dopamine signaling could be altered by striatal Foxp2 dysregulation remains elusive.

Even when reduced aggressive-like behaviour in R6/1-Foxp2 mice was not rescued, R6/1-Foxp2 mice were engaged in more fights than R6/1-GFP mice, suggesting that Foxp2 could modulate these alterations. In fact, *Foxp2* heterozygous mice reveal significant deficits in male territorial aggression by displaying smaller number of attacks, and shorter durations in the fights in a resident-intruder task (Herrero et al., 2021). Counterintuitively, juvenile 3-4-week-old R6/1 mice did not recapitulate hyperlocomotive behaviour, or hyperactivity in the running wheels during dark cycle (disruption of locomotor circadian rhythms). These negative results prevented us of having conclusions about the role of Foxp2 in hyperlocomotive or circadian rhythms alterations in juvenile R6/1 mice. We discarded that the loss of phenotype may arise as a result from the surgery intervention, since the protocol was systematically followed as described elsewhere (Janus & Golde, 2014) to ensure the survival and the proper development of the pups. We hypothesized that surgery in WT and R6/1 pups could imply a source of stress that could impact in locomotion and circadian rhythmicity, since both dimensions have been shown to be sensitive to stress (Metz et al., 2001; Sturman et al., 2018).

Regarding histopathological changes, we described for the first time a reduction of the spine density in the striatum of the juvenile R6/1 mice as described in advanced stages (Spires et al., 2004). Foxp2 overexpression successfully delayed the onset of dendritic spine pathology in the striatum of R6/1 mice by increasing dendritic spine density in striatal neurons from R6/1 mice reaching similar levels to WT mice dendritic spine density. This data is consistent with previous findings in the literature suggesting Foxp2 as a positive regulator of spines in several regions and animal models (Chen et al., 2016; Enard et al., 2009). As some of the psychiatric alterations observed in juvenile R6/1 animals such as aggression or impulsivity are related to GABAergic and dopaminergic neurotransmission (Jupp et al., 2013), we aimed to explore if behavioral psychiatric-like deficits could be related to synaptic or circuits

alterations, and to study whether Foxp2 could regulates such disturbances. We checked protein levels of $GABA_A\alpha1$, $GABA_A\alpha2$ and $GABA_A\beta3$, p-PKA cat, p-PKA substrates and tyrosine hydroxylase, but we did not observe significant changes between groups. Among the reasons for the lack of significant changes could be that changes in the receptors and synaptic markers at these early ages are subtle, or inexistent. First evidence of GABA neurotransmission dysregulation has been reported in the presymptomatic 8-week-old R6/1 mice, which showed an increased number of clusters containing the α2 subunit followed by a decreased expression in late stages (Du et al., 2017). Additionally, it has been described a global increase of α1 subunit expression in the MSN neuropil of symptomatic R6/2 at 12-week-old (Cepeda et al., 2004).

Finally, a proteomic analysis was performed to identify the putative molecular targets regulated by Foxp2 which show a significant relationship with behavioural changes described before. We aimed to interrogate protein expression in the striatum of juvenile R6/1 mice and WT littermates using a mass-spectrometry assay. As expected, according to presymptomatic stage of the R6/1 mouse model, we found subtle changes in gene expression. A total of 35 genes were differentially expressed between juvenile R6/1-GFP and WT-GFP, 19 of the aberrantly regulated candidate proteins were downregulated, and 16 were upregulated. Most of the altered genes are related with cytoskeleton dynamics as trafficking, actin filament and GTPase activity. From this result, we suggest that early decrease in spine dendritic density might be associated with dysregulation of these synaptic markers, given that all the synaptic processes mentioned before are a keystone in the formation and stabilization of spine (Penzes & Cahill, 2012). Interestingly, Arhgap4, Sez6l2 and Tceal1 are associated with schizophrenia, Aldh1a, Dpp6, Dpysl4, Scarb2 and Sez6l2 are associated with risk-taking behavior, while Arhgef10l is related to insomnia. Interestingly, most of the aberrantly regulated candidate proteins were restored with Foxp2 overexpression, only 2 candidate proteins remained altered and changed expression of 6 new genes appeared as a secondary effect of Foxp2 overexpression. This broad recovery on protein expression observed in R6/1-Foxp2 mice is in line with previous studies reporting an important role for Foxp2 in neuropsychiatric disorders.

In summary, we have described early postnatal behavioral and molecular changes in the juvenile R6/1 strongly associated with early dysregulation of striatal Foxp2 levels. Importantly, some of these changes can be reversed by striatal Foxp2 overexpression, probably by restoring synaptic plasticity and general alterations in protein expression (Figure 58).

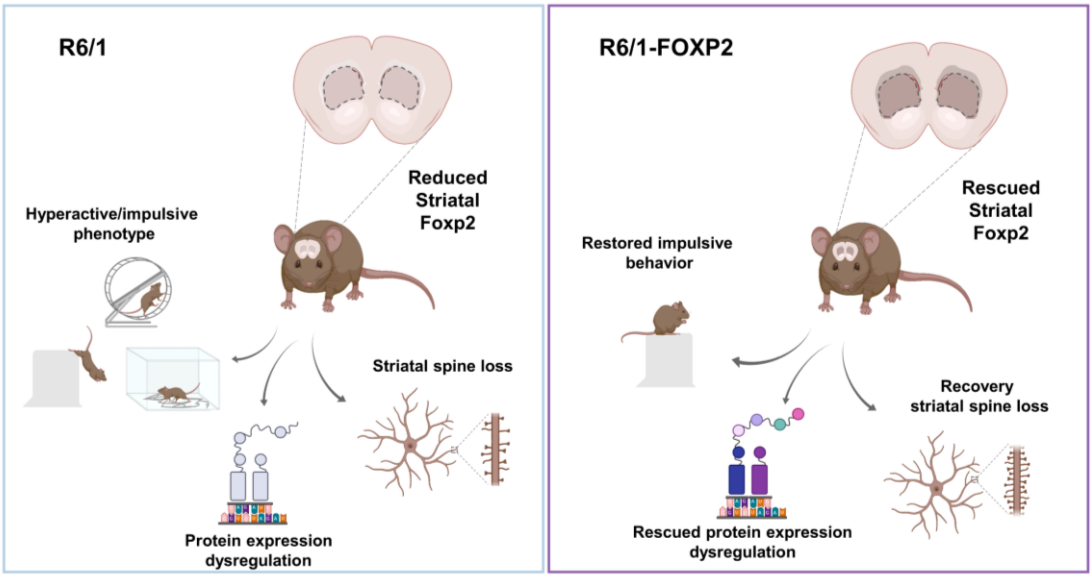


Figure 58. Recovery of striatal Foxp2 expression levels and its effects in behavioral and molecular alterations in juvenile R6/1 mice. Early dysregulation of striatal Foxp2 correlates with behavioral and molecular changes in the R6/1 mice (left panel). Recovery of striatal Foxp2 levels restores impulsivity levels in the juvenile R6/1 mice along with dendritic spine density and transcriptional regulation (right panel).

2. Unravelling the contribution of Foxp2 to the thalamostriatal circuit dysfunction and neuropathology, and the associated HD sensory-motor phenotype.

Striatum disconection from its main afferents is a core feature in HD. Both, HD patients and mouse models' striatum undergoes into a progressive depletion of the synaptic wiring with its excitatory main inputs (Bohanna et al., 2011; Cabanas et al., 2017; Dogan et al., 2015; Fernández-García et al., 2020; Gatto & Weissmann, 2022; Hintiryan et al., 2016). In addition, neurotransmission dysregulation, which is preceded by signaling dysregulation, correlates with the onset of the symptoms in the R6/2 mouse model (Cepeda et al., 2003). In this issue, cortico- and nigro-striatal pathways have received greater attention, in fact, the study of potential treatments in HD have been oriented to the re-establishment of these circuits. Nonetheless, the prescription of tetrabenazine, a dopamine pathway inhibitor indicated for the treatment of hyperkinetic movements (Marshall, 2006; Paleacu et al., 2004) has shown extrapyramidal side effects such parkinsonism and bradykinesia and worsening of psychiatric symptoms as depression, insomnia, and anxiety along with increased risk of suicidality (Claassen et al., 2018; Dalby, 1969; Elena, 2018; Guay, 2010; Jankovic & Beach, 1997). Further, pharmacological approaches targeting glutamatergic system or selective antagonism

of NMDAR has consistently shown a lack of efficacy in the improvement of symptoms and/or shown subtle effects in slow down progression of the disease in clinical trials and animal studies (Kieburtz et al., 1996; Landwehrmeyer et al., 2007; Lee et al., 2006; Seppi et al., 2001; The Huntington Study, 2001), or even worsens cognitive and psychiatric symptoms (Murman et al., 1997). Moreover, amantadine, a non-competitive NMDA antagonist suggested as therapeutic alternative for tetrabenazine in the treatment of chorea in HD (Armstrong & Miyasaki, 2012) has proved little improvement in patients, overall it is not effective reducing chorea in HD (Lucetti et al., 2002; Metman et al., 2002; O'Suilleabhain & Dewey, 2003).

This scenario implicates that not only the connections between the striatum and the cortex could be relevant for the symptoms observed in HD, but other circuits may be involved. We found that thalamostriatal alterations could play a relevant role with Foxp2 as a potential master molecule regulating these events. First, in our studies we confirmed the cortico-striatal disconection at symptomatic stages previously showed in other studies (Cepeda et al., 2003; Fernández-García et al., 2020; Hong et al., 2012; Joshi et al., 2009). Interestingly, we also were capable to demonstrate the disruption of thalamostriatal afferent connectivity at symptomatic stages in the R6/1 mice, corroborating the loss of thalamostriatal synaptic inputs already described in the zQ175 mouse model since early stages (Deng et al., 2013, 2014). Paradoxically, the study of the thalamus and its connections in HD has been poorly addressed. Thalamostriatal excitatory terminals represent the 40% of the overall excitatory drive incoming to the striatum (Lei et al., 2013). Additionally, thalamostriatal and corticostriatal afferents differs in their synapse's properties, and in the modulation of their output targets (J. Ding et al., 2008; Y. Smith et al., 2004). This differential synaptic modulation of thalamostriatal projections might suggest a distinctive role for the thalamus in synaptic plasticity, and particularly in the context of HD (Parievsky et al., 2017). Recently, it has been reported that thalamostriatal afferents contribute to the acquisition and performance of sequenced motor patterns by targeting dorsal striatum, which is implicated in motor learning and coordination (Díaz-Hernández et al., 2018). Moreover, the loss of glutamate signaling from the thalamus to the dorsal striatum compromises motor function in mice, resulting in the impairment in motor coordination tasks such as the rotarod and beam-walk tests (Melief et al., 2018). Remarkably, these motor deficits resemble HD-associated motor phenotype. Therefore, we suggested that impairment of motor skills in the R6/1 could be related to a disfunction of thalamostriatal projections.

As hypothesized, Foxp2 levels in the thalamus of the R6/1 mice were downregulated from 8, 12 and 20-week-old, recapitulating, at least in part, the early dysregulation observed in the striatum and cortex of R6/1 mice. Our colocalization studies indicated that Foxp2 staining showed just a subtle co-localization with mHtt. This result confirmed our hypothesis that additional interplaying mechanisms caused by mHtt are responsible for Foxp2 dysregulation, including but not only by sequestration by mHtt aggregates (Dunah et al., 2002; Yu et al., 2002).

As previously mentioned, Foxp2 plays a fundamental role in motor skill learning, synaptic plasticity and wiring, and coherent modulation of subcortical regions activity (French et al., 2012; Grozer et al., 2008). Moreover, Foxp2 recovery in striatum has already showed a significant efficacy in restoring HD-associated phenotype (Hachigian et al., 2017). Altogether, these data highlight the potential promising therapeutic effects of Foxp2 in thalamostriatal dysfunction and motor-sensory deficits in HD.

In our rescue studies over-expressing Foxp2 we first observed a decline of the exploratory behavior in R6/1 mice by showing a reduction in the time of supported and unsupported rearings, in accordance with previous studies in which exploration was significantly decreased in mouse models of HD (Clifford et al., 2002; Rudenko et al., 2009). Nevertheless, Foxp2 overexpression resulted ineffective in the restoration of these deficits. As already mentioned, transgenic R6/1 mouse model shows sensory deficits in a barrel cortex-dependent sensory-discrimination learning task at presymptomatic ages (Mazarakis et al., 2005). As barrel cortex-dependent sensory-discrimination are mediated by ventrolateral thalamic-cortical projections (El-Boustani et al., 2020), we hypothesized that restoration of Foxp2 levels in the ventrolateral thalamus could mitigate these alterations. Indeed, R6/1-Foxp2 showed an improvement in a sensory-whisker discrimination task suggesting that the recovery of Foxp2 thalamic levels fully and specifically recovers sensory-whisker discrimination deficits in the R6/1 mice. In accordance with these findings, a previous study revealed that a Foxp2 loss of function resulted in a substantial shortening of thalamocortical projections. Furthermore, as sensory-whisker discrimination is built on the integrity of thalamus and somatosensory cortex barreloids (Petersen, 2007; van der Loos, 1976), when these areas were examined, heterozygous Foxp2 mice showed morphological changes in both, the ventrolateral thalamus, and the cerebral cortex, suggesting that disruption of barreloid patterns in the thalamus leads to disruption of barrel patterns in the cerebral cortex (Ebisu et al., 2017). All these data suggest the involvement of Foxp2 in the integrity of thalamus and regulation of thalamocortical projection patterns, which seems to be essential for the preservation of

whisker sensory perception. Conversely, in the evaluation of tactile perception in the spontaneous place preference test, we reported an absence of significant tactile perception disturbances in the R6/1 mice, although some tendency towards a subtle impairment can be observed in the R6/1-GFP, whereas R6/1-Foxp2 showed a tendency towards improvement of tactile perception, suggesting a therapeutic role for Foxp2 in perception-related thalamocortical pathway. Interestingly, it has been reported that HD patients at early stages of the disease preserve subjective perception of sensation but impairment of sensorimotor integration (Mirallave et al., 2017). In our study, the lack of differences between mutant mice and WT controls might be due to the simplicity of the test, which has been designed as a passive task and integration of stimulus-responses is not particularly required.

Motor learning and coordination deficits in the R6/1 mice during the rotarod perfomance task were fully corrected after restoration of thalamic Foxp2 levels in the R6/1 mice. Motor learning and coordination are substantially affected in the R6/1 mouse model as described elsewhere (Barriga et al., 2017; Creus-Muncunill et al., 2019). In our study, R6/1-GFP mice exhibited a functional decline in the learning and performance of sequenced motor patterns, which remained consistently across the trials. On the contrary, R6/1-Foxp2 mice showed a significant improvement in motor acquisition and perfomance reaching similar levels to WT controls. These relevant findings led us to consider that motor learning and coordination deficits in the R6/1 mouse model might be highly regulated by the thalamostriatal pathway, and that this thalamostriatal pathway is partially or completely restored by the rescue of the Foxp2 levels in the thalamus. In contrast, Foxp2 overexpression was unable to improve the altered performance of the R6/1 mice in the vertical pole test. Interestingly, although the vertical pole test is used to assess the motor coordination during turning behavior in mice, the task is supposed to be highly sensitive to the nigrostriatal pathway. Furthermore, this test has been well established for examining bradykinesia or the effects of an injection of 1-methyl4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice (Hölter & Glasl, 2011; Matsuura et al., 1997; Ogawa et al., 1985; Tasaki et al., 1991), which is commonly used as a model of Parkinson's disease (Arai et al., 1990). In our study, the recovery of thalamic Foxp2 levels exerted effects in behavioral deficits which seem to be based on specific thalamic projections, for example, by the cortical and striatal efferents. Altogether, we can conclude that R6/1 mouse-behavioral deficits are age-dependent and region-specific like what is observed in HD patients and other HD mouse models (Cao et al., 2019; K. L. Harris et al., 2019; Hernandez et al., 2021; Quirion & Parsons, 2019; Rangel-Barajas & Rebec, 2016; Sapp et al., 2020). In this thesis, we demonstrated that deficits in sensory-whisker discrimination and rotarod

perfomance in R6/1 mice seems to be highly dependent on thalamocortical and thalamostriatal circuit dysfunction mediated by a loss of Foxp2 expression, and that the recovery of such Foxp2 reduced levels appears to alleviate these disturbances.

In addition to the rescue of sensory-motor disturbances in the symptomatic R6/1 mice, we described structural plasticity changes in striatum and somatosensory cortex of mutant mice after Foxp2 thalamic overexpression. First, we confirmed a decrease in dendritic spine density in MSNs of the dorsal striatum as previously reported (Ferrante et al., 1991; Graveland et al., 1985; Klapstein et al., 2001; Spires et al., 2004). Additionally, we found a reduction in the dendritic spine of L4 stellae cortical in somatosensory cortex similar to those described in the barrel cortical neurons of R6/2 mouse model (Murmu et al., 2013, 2015). Interestingly, changes on structural plasticity provoked by Foxp2 overexpression in the thalamus were demonstrated by a significantly improvement of dendritic spine density in MSNs of the dorsal striatum and L4 stellae barrel cortical neurons of transduced R6/1 mice. Genetic manipulations of Foxp2 levels have extensively proven the role of this transcription factor in the positive regulation of spine density in several brain regions and species (Y.-C. Chen et al., 2016; Druart et al., 2020; Enard et al., 2009; Schulz et al., 2010). Nevertheless, in this part of our study plasticity-induced changes emerged from the potential modulation of Foxp2 in thalamocortical and thalamostriatal pathways in HD. The involvement of Foxp2 in these excitatory pathways is still to be revealed, but some inferences of potential mechanisms can be deduced from its role in the excitatory corticostriatal pathway. Disruption of Foxp2 induces major changes in corticostriatal circuitry by affecting long term plasticity, dendritic spine density, neuronal activity modulation, propagation of corticostriatal neuronal firing and excitatory/inhibitory balance in the striatum (French et al., 2012; Groszer et al., 2008; Murugan et al., 2013; van Rhijn et al., 2018). Whether similar changes can be occurring in thalamostriatal and thalamocortical in HD is unclear, but these pathways deserve more research.

Histological analyses revealed macroscopic neuropathological changes in several regions of the R6/1 mice. A dramatic striatal atrophy, with reduction of thalamus volume and cortical shrinkage were observed in the R6/1 mouse model, which faithfully recapitulates the pattern of selective brain atrophy already described in HD patients and mouse models (Crevier-Sorbo et al., 2020; Gray et al., 2008; Sotrel et al., 1991; van Dellen et al., 2000; van Raamsdonk et al., 2005; Vonsattel et al., 1985; Vonsattel et al., 2008, 2011). Interestingly, Foxp2 thalamic overexpression entirely restored ventrolateral thalamus degeneration in the R6/1 mouse and partially rescued striatal degeneration, which conversely resulted ineffective in the rescue of

the somatosensory cortex thickness loss in R6/1 mouse model. In the pursue of the underlying potential mechanisms behind these results, we found outstanding data regarding Foxp2 and the neuropathological consequences of its loss of function. A bilateral reduction in the volume of the caudate nucleus has been described in patients with speech and language disorder, which is caused by a mutation in FOXP2 gene (Vargha-Khadem et al., 1998). Deletion of the human VLDLR gene, which is a major putative target of FOXP2, has been discovered in patients, in which the cerebellar content is missing (Boycott et al., 2005; Ozcelik et al., 2008). Moreover, during mice development Foxp2 becomes essential in thalamic patterning given that its loss of function induces a substantial reduction of the ventral posterior nucleus of thalamus (Ebisu et al., 2017). Here, the mechanism by which Foxp2 overexpression partially delayed the neurodegeneration of the striatum is, to our knowledge, still unknown.

In HD, the progressive cortical loss of BDNF has been classically identified as one of the main sources underlying striatal neurodegeneration (Baquet et al., 2004; Canals et al., 2004). However, although the major source of BDNF to the striatum is provided by the cortex (Altar et al., 1997), it is known that thalamic projections constitute another supply of neurotrophic support to striatum (Conner et al., 1997). On top of this, two studies have shown an important reduction of *Bdnf* mRNA expression in a thalamostriatal nuclei of R6/2 mice, corresponding to significant atrophy and reduced number of striatal neurons (Samadi et al., 2013; Wang et al., 2021). Moreover, a chronic pharmacologic treatment targeting thalamostriatal projections rescued BDNF expression and D2 MSNs in the HD mouse model (Wang et al., 2021). These data suggest that in addition to cortical afferents, anterograde thalamostriatal BDNF trophic support may therefore also play an important role in survival of striatal neurons in HD. In our case, in despite of these significant data, we discarded a potential rescue of BDNF transport or increased levels since BDNF expression in our main thalamic target, the ventral posterior nucleus, seems to be particularly absent (Conner et al., 1997).

Synapse loss and aberrant plasticity are major contributors to the onset and progression of several neurodegenerative diseases (Chang et al., 2019; Chen et al., 2018; Pradhan et al., 2019; Selkoe, 2002). In some of these diseases, the thalamostriatal projections appear to be particularly affected and correlate with motor disorders (Crevier-Sorbo et al., 2020; Parker et al., 2016). As we previously discussed, certain motor skills that are affected in the R6/1 mice depend on the integrity of the thalamostriatal circuit (Melief et al., 2018). Based on these findings, we proposed that the delay in striatal neurodegeneration and plasticity-induced

changes in the R6/1-Foxp2 mice may arise from the remodeling of thalamostriatal projections in HD by Foxp2 overexpression, starting with minor changes in synaptic plasticity as an increase of the number of dendritic spines and progressing to macroscopic changes as a correction of the striatal volume. Based on this hypothesis, we have planned to perform in the close future a subset of parallel experiments including *in vivo* microdialysis and electrophysiological techniques to functionally assess thalamostriatal and thalamocortical pathways in R6/1 mice, and further examine the neuroprotective effects of Foxp2 overexpression.

A more detailed analysis of neurochemical profiles from R6/1 mice and controls WT transduced with Foxp2 can provide further relevant information about the plasticity-induced effects of Foxp2 overexpression in our HD mouse model. So far, a first assessment of thalamocortical projections showed a substantial decreased in VGluT2+ terminals in R6/1 mice compared to WT controls, whereas PSD-95 clusters were spared. Altogether, these data suggested a severe loss of thalamocortical inputs in symptomatic R6/1 mice, and that presynaptic excitatory sites in the barrel cortex, rather than postsynaptic sites, are disrupted in the symptomatic R6/1 mice. VGluT2 levels in thalamocortical terminals of Foxp2 transduced R6/1 mice were not significantly different compared to WT controls, and showed a promising tendency towards increase, although did not reach significant levels. Altogether, we assumed that Foxp2 overexpression in the ventrolateral thalamus could be a helpful approach to tackle synaptic deficits in the R6/1 mouse model, but further analysis needs to be done.

Briefly, we finally described that knockdown of Foxp2 in the thalamus of WT mice resulted in the development of HD-associated behaviors including a decreased exploratory behavior and decline in motor perfomance, along with whisker-sensory disturbances. These results are in line with other studies showing that genetic manipulation of Foxp2 leads to motor impairments which resemble to those observed in HD (French et al., 2012; Hachigian et al., 2017). However, in our study we demonstrated that motor and whisker sensory perception impairment might arise from the single Foxp2 disruption in the ventrolateral thalamus, suggesting the relevance of Foxp2 in thalamostriatal and thalamocortical circuits in HD, and the highly specificity of these circuits as interplaying mechanisms underlying HD-behavioral phenotype (Figure 59).

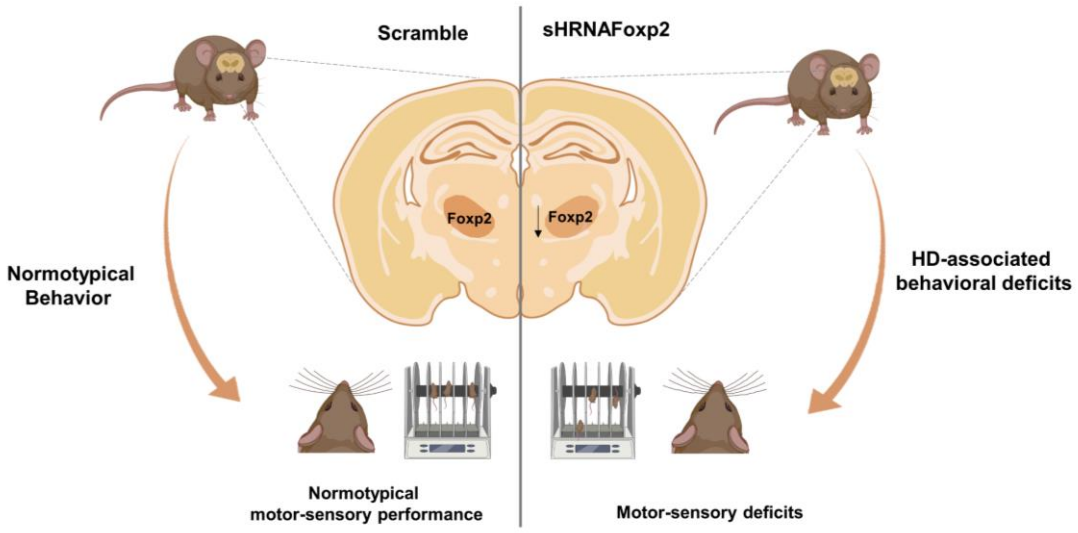


Figure 59. Knockdown of Foxp2 mimics HD-associated phenotype. Normotypical motor-sensory responses performed by WT mice (left). Silencing of thalamic Foxp2 levels recapitulated HD-associated phenotype (right).

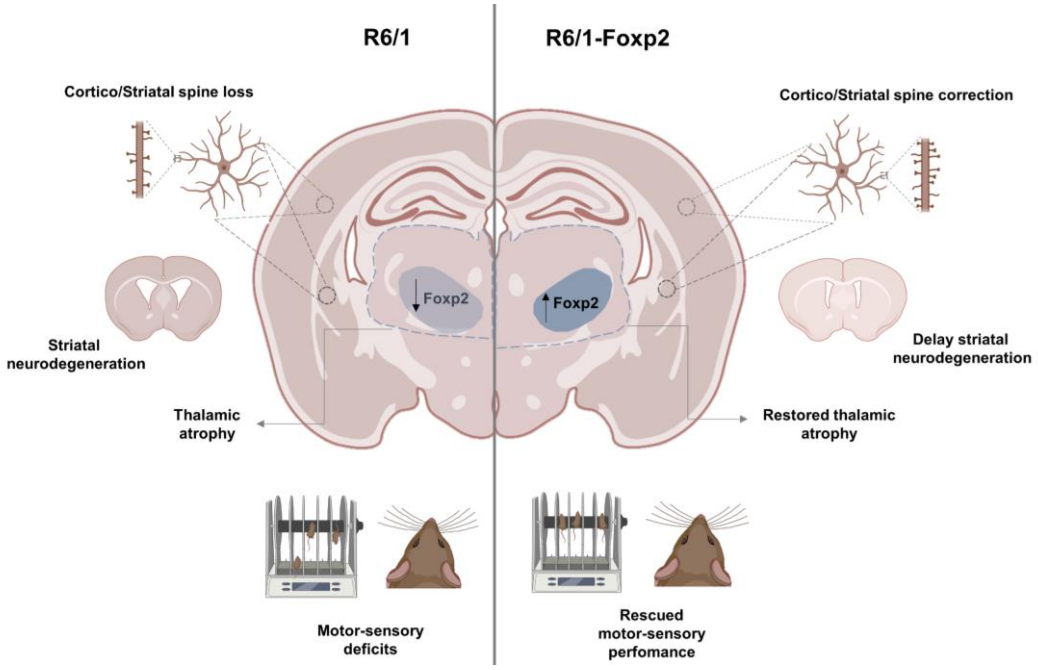


Figure 60. Rescued of thalamic Foxp2 expression levels and its effects in behavioral and molecular alterations in symptomatic R6/1 mice. Decreased thalamic Foxp2 expression correlated with behavioral and neuropathological changes in the symptomatic R6/1 mice (left). Recovery of thalamic Foxp2 levels restored motor and sensory deficits in the R6/1 mice, likely by restoring spine dendritic loss and neuropathology (right).

In summary, we proposed that HD-associated phenotype emerges from dysfunctions located in the thalamostriatal and thalamocortical circuitry and provided strong evidence of the potential therapeutic effects caused by a thalamic Foxp2 recovery in the improvement of HD-associated phenotypes, likely by restoring synaptic plasticity and delaying thalamic and striatal neurodegeneration (Figure 60).

CONCLUSIONS

1. Juvenile R6/1 mouse model exhibits an early behavioural phenotype, characterized by hyperlocomotive and impulsive-like behavior, less aggressive-like behavior in conjunction with altered locomotor circadian rhythms.
2. R6/1 early behavioural phenotype correlates with an early and specific dysregulation of Foxp2 levels expression in dorsal striatum.
3. Normalization of striatal Foxp2 levels expression in the juvenile R6/1 mouse model restores impulsivity levels, likely by rescuing protein expression dysregulation and synaptic plasticity impairments.
4. Thalamostriatal synaptic inputs are decreased in symptomatic R6/1 mouse and correlate with the downregulation of thalamic Foxp2 expression levels and the onset of motor phenotypes.
5. Genetic normalization of thalamic Foxp2 levels in the symptomatic R6/1 mouse model rescues motor-sensory disturbances, likely by restoring synaptic plasticity and connectivity.
6. Ventrolateral thalamic Foxp2 silencing recapitulates some HD-associated phenotypes.

REFERENCES

ACMG/ASHG statement. Laboratory guidelines for Huntington disease genetic testing. The American College of Medical Genetics/American Society of Human Genetics Huntington Disease Genetic Testing Working Group. (1998). American Journal of Human Genetics, 62(5), 1243. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1377103/

Adam, I., Mendoza, E., Kobalz, U., Wohlgemuth, S., & Scharff, C. (2016). FoxP2 directly regulates the reelin receptor VLDLR developmentally and by singing. Molecular and Cellular Neuroscience, 74, 96–105. https://doi.org/10.1016/J.MCN.2016.04.002

Adam, I., Mendoza, E., Kobalz, U., Wohlgemuth, S., & Scharff, C. (2017). CNTNAP2 is a direct FoxP2 target in vitro and in vivo in zebra finches: complex regulation by age and activity. Genes, Brain and Behavior, 16(6), 635–642. https://doi.org/10.1111/GBB.12390

Adamczyk, A., Mejias, R., Takamiya, K., Yocum, J., Krasnova, I., Calderon, J., Lud Cadet, J., Huganir, R., Pletnikov, M., Wang, T., & Author, C. (2012). GluA3-deficiency in Mice is Associated with Increased Social and Aggressive Behavior and Elevated Dopamine in Striatum. Behav Brain Res, 229(1), 265–272. https://doi.org/10.1016/j.bbr.2012.01.007

Aggarwal, M., Duan, W., Hou, Z., Rakesh, N., Peng, Q., Ross, C. A., Miller, M. I., Mori, S., & Zhang, J. (2012). Spatiotemporal mapping of brain atrophy in mouse models of Huntington's disease using longitudinal in vivo magnetic resonance imaging. Neuroimage, 60(4), 2086. https://doi.org/10.1016/J.NEUROIMAGE.2012.01.141

Alarcón, M., Abrahams, B. S., Stone, J. L., Duvall, J. A., Perederiy, J. v., Bomar, J. M., Sebat, J., Wigler, M., Martin, C. L., Ledbetter, D. H., Nelson, S. F., Cantor, R. M., & Geschwind, D. H. (2008). Linkage, Association, and Gene-Expression Analyses Identify CNTNAP2 as an Autism-Susceptibility Gene. The American Journal of Human Genetics, 82(1), 150–159. https://doi.org/10.1016/J.AJHG.2007.09.005

Alberch, J., Pérez-Navarro, E., & Canals, J. M. (2002). Neuroprotection by neurotrophins and GDNF family members in the excitotoxic model of Huntington's disease. Brain Research Bulletin, 57(6), 817–822. https://doi.org/10.1016/S0361-9230(01)00775-4

Albin, R. L., Qin, Y., Young, A. B., Penney, J. B., & Chesselet, M. -F. (1991). Preproenkephalin messenger RNA—containing neurons in striatum of patients with symptomatic and presymptomatic huntington's disease: An in situ hybridization study. Annals of Neurology, 30(4), 542–549. https://doi.org/10.1002/ANA.410300406

Ali, N. J., & Levine, M. S. (2006). Changes in expression of N-methyl-D-aspartate receptor subunits occur early in the R6/2 mouse model of Huntington's disease. Developmental Neuroscience, 28(3), 230–238. https://doi.org/10.1159/000091921

Altar, C. A., Cai, N., Bliven, T., Juhasz, M., Conner, J. M., Acheson, A. L., Lindsay, R. M., & Wiegand, S. J. (1997). Anterograde transport of brain-derived neurotrophic factor and its role in the brain. Nature 1997 389:6653, 389(6653), 856–860. https://doi.org/10.1038/39885

Ambrose, C. M., Duyao, M. P., Barnes, G., Bates, G. P., Lin, C. S., Srinidhi, J., Baxendale, S., Hummerich, H., Lehrach, H., Altherr, M., Wasmuth, J., Buckler, A., Church, D., Housman, D., Berks, M., Micklem, G., Durbin, R., Dodge, A., Read, A., … MacDonald, M. E. (1994). Structure and expression of the Huntington's disease gene: Evidence against simple inactivation due to an expanded CAG repeat. Somatic Cell and Molecular Genetics, 20(1), 27–38. https://doi.org/10.1007/BF02257483

Amen, D. G., Stubblefield, M., Carmichael, B., & Thisted, R. (1996). Brain SPECT findings and aggressiveness. Annals of Clinical Psychiatry, 8(3), 129–137. https://doi.org/10.3109/10401239609147750

REFERENCES

Anderson, K. E., & Marder, K. S. (2001). An Overview of Psychiatric Symptoms in Huntington's Disease.

Andrade, M. A., & Bork, P. (1995). HEAT repeats in the Huntington's disease protein. In Nature Genetics (Vol. 11, Issue 2, pp. 115–116). Nat Genet. https://doi.org/10.1038/ng1095-115

Andre, V. M., Fisher, Y. E., & Levine, M. S. (2011). Altered Balance of Activity in the Striatal Direct and Indirect Pathways in Mouse Models of Huntington's Disease. Frontiers in Systems Neuroscience, 0(JUNE 2011), 46. https://doi.org/10.3389/FNSYS.2011.00046

Arai, N., Misugi, K., Goshima, Y., & Misu, Y. (1990). Evaluation of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated C57 black mouse model for parkinsonism. Brain Research, 515(1–2), 57–63. https://doi.org/10.1016/0006-8993(90)90576-W

Ariano, M. A., Aronin, N., Difiglia, M., Tagle, D. A., Sibley, D. R., Leavitt, B. R., Hayden, M. R., & Levine, M. S. (2002). Striatal neurochemical changes in transgenic models of Huntington's disease. Journal of Neuroscience Research, 68(6), 716–729. https://doi.org/10.1002/JNR.10272

Armstrong, M. J., & Miyasaki, J. M. (2012). Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease. Neurology, 79(6), 597–603. https://doi.org/10.1212/WNL.0B013E318263C443

Arnoux, I., Willam, M., Griesche, N., Krummeich, J., Watari, H., Offermann, N., Weber, S., Dey, P. N., Chen, C., Monteiro, O., Buettner, S., Meyer, K., Bano, D., Radyushkin, K., Langston, R., Lambert, J. J., Wanker, E., Methner, A., Krauss, S., … Stroh, A. (2018). Metformin reverses early cortical network dysfunction and behavior changes in Huntington's disease. ELife, 7. https://doi.org/10.7554/eLife.38744

Aron, A. R., Dowson, J. H., Sahakian, B. J., & Robbins, T. W. (2003). Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry, 54(12), 1465–1468. https://doi.org/10.1016/S0006-3223(03)00609-7

Arzberger, T., Krampfl, K., Leimgruber, S., & Weindl, A. (1997). Changes of NMDA receptor subunit (NR1, NR2B) and glutamate transporter (GLT1) mRNA expression in Huntington's disease - An in situ hybridization study. Journal of Neuropathology and Experimental Neurology, 56(4), 440–454. https://doi.org/10.1097/00005072-199704000-00013

Augood, S. J., Faull, R. L. M., Love, D. R., & Emson, P. C. (1996). Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: A detailed cellular in situ hybridization study. Neuroscience, 72(4), 1023–1036. https://doi.org/10.1016/0306-4522(95)00595-1

Augood, S. J., Faull, R. L. M., & Emson, P. C. (1997). Dopamine D1 and D2 receptor gene expression in the striatum in Huntington's disease. Annals of Neurology, 42(2), 215–221. https://doi.org/10.1002/ana.410420213

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

Bakkaloglu, B., O'Roak, B. J., Louvi, A., Gupta, A. R., Abelson, J. F., Morgan, T. M., Chawarska, K., Klin, A., Ercan-Sencicek, A. G., Stillman, A. A., Tanriover, G., Abrahams, B. S., Duvall, J. A., Robbins, E. M., Geschwind, D. H., Biederer, T., Gunel, M., Lifton, R. P., & State, M. W. (2008). Molecular Cytogenetic Analysis and Resequencing of Contactin Associated Protein-Like 2 in

Autism Spectrum Disorders. American Journal of Human Genetics, 82(1), 165–173. https://doi.org/10.1016/j.ajhg.2007.09.017

Bäckman, L., Robins-Wahlin, T. B., Lundin, A., Ginovart, N., & Farde, L. (1997). Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes. Brain, 120(12), 2207–2217. https://doi.org/10.1093/BRAIN/120.12.2207

Balci, F., Day, M., Rooney, A., & Brunner, D. (2009). Disrupted Temporal Control in the R6/2 Mouse Model of Huntington's Disease. Behavioral Neuroscience, 123(6), 1353–1358. https://doi.org/10.1037/A0017650

Baquet, Z. C., Gorski, J. A., & Jones, K. R. (2004). Early Striatal Dendrite Deficits followed by Neuron Loss with Advanced Age in the Absence of Anterograde Cortical Brain-Derived Neurotrophic Factor. Journal of Neuroscience, 24(17), 4250–4258. https://doi.org/10.1523/JNEUROSCI.3920-03.2004

Barriga, G. G. D., Giralt, A., Anglada-Huguet, M., Gaja-Capdevila, N., Orlandi, J. G., Soriano, J., Canals, J. M., & Alberch, J. (2017). 7,8-dihydroxyflavone ameliorates cognitive and motor deficits in a Huntington's disease mouse model through specific activation of the PLCγ1 pathway. Human Molecular Genetics, 26(16), 3144–3160. https://doi.org/10.1093/hmg/ddx198

Bassi, S., Tripathi, T., Monziani, a., Di Leva, F., & Biagioli, M. (2017). Epigenetics of Huntington's Disease. Advances in Experimental Medicine and Biology, 978, 277–299. https://doi.org/10.1007/978-3-319-53889-1_15

Bates, G. P., Dorsey, R., Gusella, J. F., Hayden, M. R., Kay, C., Leavitt, B. R., Nance, M., Ross, C. A., Scahill, R. I., Wetzel, R., Wild, E. J., & Tabrizi, S. J. (2015). Huntington disease. Nature Reviews Disease Primers 2015 1:1, 1(1), 1–21. https://doi.org/10.1038/NRDP.2015.5

Beal, M. F., Kowall, N. W., Swartz, K. J., Ferrante, R. J., & Martin, J. B. (1989). Differential sparing of somatostatin-neuropeptide y and cholinergic neurons following striatal excitotoxin lesions. Synapse, 3(1), 38–47. https://doi.org/10.1002/SYN.890030106

Beal, M. F., Ferrante, R. J., Swartz, K. J., & Kowall, N. W. (1991). Chronic quinolinic acid lesions in rats closely resemble Huntington's disease. Journal of Neuroscience, 11(6), 1649–1659. https://doi.org/10.1523/jneurosci.11-06-01649.1991

Beal, M. F., Brouillet, E., Jenkins, B. G., Ferrante, R. J., Kowall, N. W., Miller, J. M., Storey, E., Srivastava, R., Rosen, B. R., & Hyman, B. T. (1993). Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. Journal of Neuroscience, 13(10), 4181–4192. https://doi.org/10.1523/jneurosci.13-10-04181.1993

Becker, L., Kutz, D. F., & Voelcker-Rehage, C. (2016). Exercise-induced changes in basal ganglia volume and their relation to cognitive performance. Journal of Neurology and Neuromedicine, 1(5), 19–24. https://doi.org/10.29245/2572.942x/2016/5.1044

Beglinger, L. J., Nopoulos, P. C., Jorge, R. E., Langbehn, D. R., Mikos, A. E., Moser, D. J., Duff, K., Robinson, R. G., & Paulsen, J. S. (2005). White matter volume and cognitive dysfunction in early Huntington's disease. Cognitive and Behavioral Neurology, 18(2), 102–107. https://doi.org/10.1097/01.wnn.0000152205.79033.73

Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W., & Everitt, B. J. (2008). High impulsivity predicts the switch to compulsive cocaine-taking. Science, 320(5881), 1352–1355. https://doi.org/10.1126/science.1158136

REFERENCES

Benjamin, C. M., Adam, S., Wiggins, S., Theilmann, J. L., Copley, T. T., Bloch, M., Squitieri, F., McKellin, W., Cox, S., Brown, S. A., Kremer, H. P. H., Burgess, M., Meshino, W., Summers, A., Macgregor, D., Buchanan, J., Greenberg, C., Carson, N., Ives, E., … Hayden, M. R. (1994). Proceed with Care: Direct Predictive Testing for Huntington Disease. American Journal of Human Genetics, 55(4), 606–615. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/7942838/?tool=EBI

Benn, C. L., Slow, E. J., Farrell, L. A., Graham, R., Deng, Y., Hayden, M. R., & Cha, J.-H. J. (2007). Glutamate receptor abnormalities in the YAC128 transgenic mouse model of Huntington's disease. Neuroscience, 147(2), 354. https://doi.org/10.1016/J.NEUROSCIENCE.2007.03.010

Benn, C. L., Sun, T., Sadri-Vakili, G., McFarland, K. N., DiRocco, D. P., Yohrling, G. J., Clark, T. W., Bouzou, B., & Cha, J.-H. J. (2008). Huntingtin Modulates Transcription, Occupies Gene Promoters In Vivo, and Binds Directly to DNA in a Polyglutamine-Dependent Manner. The Journal of Neuroscience, 28(42), 10720. https://doi.org/10.1523/JNEUROSCI.2126-08.2008

Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K., & Seitelberger, F. (1973). Brain dopamine and the syndromes of Parkinson and Huntington Clinical, morphological and neurochemical correlations. Journal of the Neurological Sciences, 20(4), 415–455. https://doi.org/10.1016/0022-510X(73)90175-5

Berretta, S., Parthasarathy, H. B., & Graybiel, A. M. (1997). Local Release of GABAergic Inhibition in the Motor Cortex Induces Immediate-Early Gene Expression in Indirect Pathway Neurons of the Striatum. Journal of Neuroscience, 17(12), 4752–4763. https://doi.org/10.1523/JNEUROSCI.17-12-04752.1997

Besusso, D., Geibel, M., Kramer, D., Schneider, T., Pendolino, V., Picconi, B., Calabresi, P., Bannerman, D. M., & Minichiello, L. (2013). BDNF–TrkB signaling in striatopallidal neurons controls inhibition of locomotor behavior. Nature Communications 2013 4:1, 4(1), 1–12. https://doi.org/10.1038/ncomms3031

Bibb, J. A., Yan, Z., Svenningsson, P., Snyder, G. L., Pieribone, V. A., Horiuchi, A., Nairn, A. C., Messer, A., & Greengard, P. (2000). Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. Proceedings of the National Academy of Sciences, 97(12), 6809–6814. https://doi.org/10.1073/PNAS.120166397

Bird. (1980). Chemical pathology of Huntington's disease. Annual Review of Pharmacology and Toxicology, 20, 533–551. https://doi.org/10.1146/ANNUREV.PA.20.040180.002533

Bohanna, I., Georgiou-Karistianis, N., & Egan, G. F. (2011). Connectivity-based segmentation of the striatum in Huntington's disease: Vulnerability of motor pathways. Neurobiology of Disease, 42(3), 475–481. https://doi.org/10.1016/J.NBD.2011.02.010

Bolivar, V. J., Manley, K., & Messer, A. (2004). Early exploratory behavior abnormalities in R6/1 Huntington's disease transgenic mice. Brain Research, 1005(1–2), 29–35. https://doi.org/10.1016/J.BRAINRES.2004.01.021

Bonfoco, E., Krainc, D., Ankarcrona, M., Nicotera, P., & Lipton, S. A. (1995). Apoptosis and necrosis: Two distinct events induced, respectively, by mild and intense insults with N-methyl-D-aspartate or nitric oxide/superoxide in cortical cell cultures. Proceedings of the National Academy of Sciences of the United States of America, 92(16), 7162–7166. https://doi.org/10.1073/PNAS.92.16.7162

Bonkowsky, J. L., Wang, X., Fujimoto, E., Lee, J. E., Chien, C.-B., & Dorsky, R. I. (2008). Domain-specific regulation of foxP2 CNS expression by lef1. BMC Developmental Biology 2008 8:1, 8(1), 1–15. https://doi.org/10.1186/1471-213X-8-103

Borlongan, C. v., Koutouzis, T. K., & Sanberg, P. R. (1997). 3-Nitropropionic acid animal model and Huntington's disease. Neuroscience and Biobehavioral Reviews, 21(3), 289–293. https://doi.org/10.1016/S0149-7634(96)00027-9

Boycott, K. M., Flavelle, S., Bureau, A., Glass, H. C., Fujiwara, T. M., Wirrell, E., Davey, K., Chudley, A. E., Scott, J. N., McLeod, D. R., & Parboosingh, J. S. (2005). Homozygous Deletion of the Very Low Density Lipoprotein Receptor Gene Causes Autosomal Recessive Cerebellar Hypoplasia with Cerebral Gyral Simplification. The American Journal of Human Genetics, 77(3), 477–483. https://doi.org/10.1086/444400

Brady, R. v. (2019). Rare Disease Clinical Research Untapped potential in MENA A White Paper by Clinart MENA in collaboration with LongTaal Access live data.

Brandon, N. J., Millar, J. K., Korth, C., Sive, H., Singh, K. K., & Sawa, A. (2009). Understanding the Role of DISC1 in Psychiatric Disease and during Normal Development. Journal of Neuroscience, 29(41), 12768–12775. https://doi.org/10.1523/JNEUROSCI.3355-09.2009

Brinkman, R. R., Mezei, M. M., Theilmann, ' J, Almqvist,', E., & Hayden1, M. R. (1997). The Likelihood of Being Affected with Huntington Disease by a Particular Age, for a Specific CAG Size. Am. J. Hum. Genet, 60, 1202–1210.

Brito, V., Puigdellívol, M., Giralt, A., del Toro, D., Alberch, J., & Ginés, S. (2013). Imbalance of p75NTR/TrkB protein expression in Huntington's disease: implication for neuroprotective therapies. Cell Death & Disease 2013 4:4, 4(4), e595–e595. https://doi.org/10.1038/cddis.2013.116

Brito, V., Giralt, A., Enriquez-Barreto, L., Puigdellívol, M., Suelves, N., Zamora-Moratalla, A., Ballesteros, J. J., Martín, E. D., Dominguez-Iturza, N., Morales, M., Alberch, J., & Ginés, S. (2014). Neurotrophin receptor p75NTR mediates Huntington's disease-associated synaptic and memory dysfunction. Journal of Clinical Investigation, 124(10), 4411–4428. https://doi.org/10.1172/JCI74809

Brito, V., Giralt, A., Masana, M., Royes, A., Espina, M., Sieiro, E., Alberch, J., Castañé, A., Girault, J. A., & Ginés, S. (2019). Cyclin-Dependent Kinase 5 Dysfunction Contributes to Depressive-like Behaviors in Huntington's Disease by Altering the DARPP-32 Phosphorylation Status in the Nucleus Accumbens. Biological Psychiatry, 86(3), 196–207. https://doi.org/10.1016/J.BIOPSYCH.2019.03.001

Brooks, S. P., Janghra, N., Workman, V. L., Bayram-Weston, Z., Jones, L., & Dunnett, S. B. (2012). Longitudinal analysis of the behavioural phenotype in R6/1 (C57BL/6J) Huntington's disease transgenic mice. Brain Research Bulletin, 88(2–3), 94–103. https://doi.org/10.1016/J.BRAINRESBULL.2011.01.010

Bruce, H. A., & Margolis, R. L. (2002). FOXP2: Novel exons, splice variants, and CAG repeat length stability. Human Genetics, 111(2), 136–144. https://doi.org/10.1007/s00439-002-0768-5

Burdick, K. E., DeRosse, P., Kane, J. M., Lencz, T., & Malhotra, A. K. (2010). Association of Genetic Variation in the MET Proto-Oncogene With Schizophrenia and General Cognitive Ability. Https://Doi.Org/10.1176/Appi.Ajp.2009.09050615, 167(4), 436–443. https://doi.org/10.1176/APPI.AJP.2009.09050615

Burgold, J., Schulz-Trieglaff, E. K., Voelkl, K., Gutiérrez-Ángel, S., Bader, J. M., Hosp, F., Mann, M., Arzberger, T., Klein, R., Liebscher, S., & Dudanova, I. (2019). Cortical circuit alterations precede motor impairments in Huntington's disease mice. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-43024-w

REFERENCES

Cabanas, M., Bassil, F., Mons, N., Garret, M., & Cho, Y. H. (2017). Changes in striatal activity and functional connectivity in a mouse model of Huntington's disease. PLOS ONE, 12(9), e0184580. https://doi.org/10.1371/JOURNAL.PONE.0184580

Calabresi, P., Centonze, D., Pisani, A., Sancesario, G., Gubellini, P., Marfia, G. A., & Bernardi, G. (1998). Striatal spiny neurons and cholinergic interneurons express differential ionotropic glutamatergic responses and vulnerability: Implications for ischemia and Huntington's disease. Annals of Neurology, 43(5), 586–597. https://doi.org/10.1002/ANA.410430506

Callahan, J. W., & Abercrombie, E. D. (2011). In vivo Dopamine Efflux is Decreased in Striatum of both Fragment (R6/2) and Full-Length (YAC128) Transgenic Mouse Models of Huntington's Disease. Frontiers in Systems Neuroscience, 0(JULY 2011), 61. https://doi.org/10.3389/FNSYS.2011.00061

Campbell, D. B., Sutcliffe, J. S., Ebert, P. J., Militerni, R., Bravaccio, C., Trillo, S., Elia, M., Schneider, C., Melmed, R., Sacco, R., Persico, A. M., & Levitt, P. (2006). A genetic variant that disrupts MET transcription is associated with autism. Proceedings of the National Academy of Sciences, 103(45), 16834–16839. https://doi.org/10.1073/PNAS.0605296103

Campbell, D. B., D'Oronzio, R., Garbett, K., Ebert, P. J., Mirnics, K., Levitt, P., & Persico, A. M. (2007). Disruption of cerebral cortex MET signaling in autism spectrum disorder. Annals of Neurology, 62(3), 243–250. https://doi.org/10.1002/ANA.21180

Canals, J. M., Pineda, J. R., Torres-Peraza, J. F., Bosch, M., Martín-Ibañez, R., Muñoz, M. T., Mengod, G., Ernfors, P., & Alberch, J. (2004). Brain-Derived Neurotrophic Factor Regulates the Onset and Severity of Motor Dysfunction Associated with Enkephalinergic Neuronal Degeneration in Huntington's Disease. Journal of Neuroscience, 24(35), 7727–7739. https://doi.org/10.1523/JNEUROSCI.1197-04.2004

Cao, J. K., Viray, K., Zweifel, L., & Stella, N. (2019). Sex-dependent impaired locomotion and motor coordination in the HdhQ200/200 mouse model of Huntington's Disease. Neurobiology of Disease, 132, 104607. https://doi.org/10.1016/J.NBD.2019.104607

Cardoso, F. (2009). Huntington Disease and Other Choreas. Neurologic Clinics, 27(3), 719–736. https://doi.org/10.1016/J.NCL.2009.04.001

Carlsson, P., & Mahlapuu, M. (2002). Forkhead transcription factors: Key players in development and metabolism. In Developmental Biology (Vol. 250, Issue 1, pp. 1–23). Dev Biol. https://doi.org/10.1006/dbio.2002.0780

Casseb, R. F., D'Abreu, A., Ruocco, H. H., Lopes-Cendes, I., Cendes, F., & Castellano, G. (2013). Thalamic metabolic abnormalities in patients with Huntington's disease measured by magnetic resonance spectroscopy. Brazilian Journal of Medical and Biological Research, 46(8), 722–727. https://doi.org/10.1590/1414-431X20132332

Castillo, P. E., Janz, R., Sdhof, T. C., Tzounopoulos, T., Malenka, R. C., & Nicoll, R. A. (1997). Rab3A is essential for mossy fibre long-term potentiation in the hippocampus. Nature 1997 388:6642, 388(6642), 590–593. https://doi.org/10.1038/41574

Castro Martínez, X. H., Moltó Ruiz, M. D., Morales Marin, M. E., Flores Lázaro, J. C., González Fernández, J., Gutiérrez Najera, N. A., Alvarez Amado, D. E., Nicolini Sánchez, J. H., Castro Martínez, X. H., Moltó Ruiz, M. D., Morales Marin, M. E., Flores Lázaro, J. C., González Fernández, J., Gutiérrez Najera, N. A., Alvarez Amado, D. E., & Nicolini Sánchez, J. H. (2019). FOXP2 and language alterations in psychiatric pathology. Salud Mental, 42(6), 297–308. https://doi.org/10.17711/SM.0185-3325.2019.039

Cataldi, S., Stanley, A. T., Miniaci, M. C., & Sulzer, D. (2021). Interpreting the role of the striatum during multiple phases of motor learning. The FEBS Journal. https://doi.org/10.1111/FEBS.15908

Caviston, J. P., Ross, J. L., Antony, S. M., Tokito, M., & Holzbaur, E. L. F. (2007). Huntingtin facilitates dynein/dynactin-mediated vesicle transport. Proceedings of the National Academy of Sciences of the United States of America, 104(24), 10045–10050. https://doi.org/10.1073/pnas.0610628104

Cayzac, S., Delcasso, S., Paz, V., Jeantet, Y., & Cho, Y. H. (2011). Changes in striatal procedural memory coding correlate with learning deficits in a mouse model of Huntington disease. Proceedings of the National Academy of Sciences, 108(22), 9280–9285. https://doi.org/10.1073/PNAS.1016190108

Cepeda, C., Ariano, M. A., Calvert, C. R., Flores-Hernández, J., Chandler B, S. H., Leavitt, B. R., Hayden, M. R., & Levine, M. S. (2001). NMDA receptor function in mouse models of Huntington disease. Journal of Neuroscience Research, 66(4), 525–539. https://doi.org/10.1002/JNR.1244

Cepeda, C., Itri, J. N., Flores-Hernández, J., Hurst, R. S., Calvert, C. R., & Levine, M. S. (2001). Differential sensitivity of medium- and large-sized striatal neurons to NMDA but not kainate receptor activation in the rat. European Journal of Neuroscience, 14(10), 1577–1589. https://doi.org/10.1046/J.0953-816X.2001.01783.X

Cepeda, C., Hurst, R. S., Calvert, C. R., Hernández-Echeagaray, E., Nguyen, O. K., Jocoy, E., Christian, L. J., Ariano, M. A., & Levine, M. S. (2003). Transient and Progressive Electrophysiological Alterations in the Corticostriatal Pathway in a Mouse Model of Huntington's Disease. Journal of Neuroscience, 23(3), 961–969. https://doi.org/10.1523/JNEUROSCI.23-03-00961.2003

Cepeda, C., Starling, A. J., Wu, N., Nguyen, O. K., Uzgil, B., Soda, T., André, V. M., Ariano, M. A., & Levine, M. S. (2004). Increased GABAergic function in mouse models of Huntington's disease: Reversal by BDNF. Journal of Neuroscience Research, 78(6), 855–867. https://doi.org/10.1002/JNR.20344

Cepeda, C., Wu, N., André, V. M., Cummings, D. M., & Levine, M. S. (2007). The corticostriatal pathway in Huntington's disease. Progress in Neurobiology, 81(5–6), 253–271. https://doi.org/10.1016/j.pneurobio.2006.11.001

Cepeda, C., André, V. M., Yamazaki, I., Wu, N., Kleiman-Weiner, M., & Levine, M. S. (2008). Differential electrophysiological properties of dopamine D1 and D2 receptor-containing striatal medium-sized spiny neurons. European Journal of Neuroscience, 27(3), 671–682. https://doi.org/10.1111/J.1460-9568.2008.06038.X

Cepeda, C., Galvan, L., Holley, S. M., Rao, S. P., André, V. M., Botelho, E. P., Chen, J. Y., Watson, J. B., Deisseroth, K., & Levine, M. S. (2013). Multiple Sources of Striatal Inhibition Are Differentially Affected in Huntington's Disease Mouse Models. Journal of Neuroscience, 33(17), 7393–7406. https://doi.org/10.1523/JNEUROSCI.2137-12.2013

Cha, J. H. J., Kosinski, C. M., Kerner, J. A., Alsdorf, S. A., Mangiarini, L., Davies, S. W., Penney, J. B., Bates, G. P., & Young, A. B. (1998). Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human Huntington disease gene. Proceedings of the National Academy of Sciences of the United States of America, 95(11), 6480–6485. https://doi.org/10.1073/pnas.95.11.6480

REFERENCES

Chabout, J., Sarkar, A., Patel, S. R., Radden, T., Dunson, D. B., Fisher, S. E., & Jarvis, E. D. (2016). A Foxp2 mutation implicated in human speech deficits alters sequencing of ultrasonic vocalizations in adult male mice. Frontiers in Behavioral Neuroscience, 10(OCT). https://doi.org/10.3389/fnbeh.2016.00197

Chai, X., Fan, L., Shao, H., Lu, X., Zhang, W., Li, J., Wang, J., Chen, S., Frotscher, M., & Zhao, S. (2015). Reelin Induces Branching of Neurons and Radial Glial Cells during Corticogenesis. Cerebral Cortex, 25(10), 3640–3653. https://doi.org/10.1093/CERCOR/BHU216

Chan, E. Y. W., Luthi-Carter, R., Strand, A., Solano, S. M., Hanson, S. A., DeJohn, M. M., Kooperberg, C., Chase, K. O., DiFiglia, M., Young, A. B., Leavitt, B. R., Cha, J.-H. J., Aronin, N., Hayden, M. R., & Olson, J. M. (2002). Increased huntingtin protein length reduces the number of polyglutamine-induced gene expression changes in mouse models of Huntington's disease. Human Molecular Genetics, 11(17), 1939–1951. https://doi.org/10.1093/HMG/11.17.1939

Chang, X., Wang, J., Jiang, H., Shi, L., & Xie, J. (2019). Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels: An Emerging Role in Neurodegenerative Diseases. Frontiers in Molecular Neuroscience, 0, 141. https://doi.org/10.3389/FNMOL.2019.00141

Chen, Y.-C., Kuo, H.-Y., Bornschein, U., Takahashi, H., Chen, S.-Y., Lu, K.-M., Yang, H.-Y., Chen, G.-M., Lin, J.-R., Lee, Y.-H., Chou, Y.-C., Cheng, S.-J., Chien, C.-T., Enard, W., Hevers, W., Pääbo, S., Graybiel, A. M., & Liu, F.-C. (2016). Foxp2 Controls Synaptic Wiring of Corticostriatal Circuits and Vocal Communication by Opposing Mef2C. Nature Neuroscience, 19(11), 1513. https://doi.org/10.1038/NN.4380

Chen, S., Yu, C., Rong, L., Li, C. H., Qin, X., Ryu, H., & Park, H. (2018). Altered Synaptic Vesicle Release and Ca2+ Influx at Single Presynaptic Terminals of Cortical Neurons in a Knock-in Mouse Model of Huntington's Disease. Frontiers in Molecular Neuroscience, 11. https://doi.org/10.3389/FNMOL.2018.00478

Chiu, C.-T., Liu, G., Leeds, P., & Chuang, D.-M. (2011). Combined Treatment with the Mood Stabilizers Lithium and Valproate Produces Multiple Beneficial Effects in Transgenic Mouse Models of Huntington's Disease. Neuropsychopharmacology 2011 36:12, 36(12), 2406–2421. https://doi.org/10.1038/npp.2011.128

Chiu, Y. C., Li, M. Y., Liu, Y. H., Ding, J. Y., Yu, J. Y., & Wang, T. W. (2014). Foxp2 regulates neuronal differentiation and neuronal subtype specification. Developmental Neurobiology, 74(7), 723–738. https://doi.org/10.1002/DNEU.22166

Chrivia, J. C., Kwok, R. P. S., Lamb, N., Hagiwara, M., Montminy, M. R., & Goodman, R. H. (1993). Phosphorylated CREB binds specifically to the nuclear protein CBP. Nature, 365(6449), 855–859. https://doi.org/10.1038/365855a0

Chong, S. S., Almqvist, E., Telenius, H., LaTray, L., Nichol, K., Bourdelat-Parks, B., Goldberg, Y. P., Haddad, B. R., Richards, F., Sillence, D., Greenberg, C. R., Ives, E., van den Engh, G., Hughes, M. R., & Hayden, M. R. (1997). Contribution of DNA sequence and CAG size to mutation frequencies of intermediate alleles for Huntington disease: Evidence from single sperm analyses. Human Molecular Genetics, 6(2), 301–309. https://doi.org/10.1093/hmg/6.2.301

Ciamei, A., & Morton, A. J. (2008). Rigidity in social and emotional memory in the R6/2 mouse model of Huntington's disease. Neurobiology of Learning and Memory, 89(4), 533–544. https://doi.org/10.1016/J.NLM.2007.10.009

Ciarmiello, A., Cannella, M., Lastoria, S., Simonelli, M., Frati, L., Rubinsztein, D. C., & Squitieri, F. (2006). Brain White-Matter Volume Loss and Glucose Hypometabolism Precede the Clinical Symptoms of Huntington's Disease. Journal of Nuclear Medicine, 47(2).

Cicchetti, F., Gould, P. v., & Parent, A. (1996). Sparing of striatal neurons coexpressing calretinin and substance P (NK1) receptor in Huntington's disease. Brain Research, 730(1–2), 232–237. https://doi.org/10.1016/0006-8993(96)00307-1

Claassen, D. O., Iyer, R. G., Shah-Manek, B., DiBonaventura, M., Abler, V., & Sung, V. W. (2018). Tetrabenazine Treatment Patterns and Outcomes for Chorea Associated with Huntington Disease: A Retrospective Chart Review. Journal of Huntington's Disease, 7(4), 345–353. https://doi.org/10.3233/JHD-170286

Clifford, J. J., Drago, J., Natoli, A. L., Wong, J. Y. F., Kinsella, A., Waddington, J. L., & Vaddadi, K. S. (2002). Essential fatty acids given from conception prevent topographies of motor deficit in a transgenic model of Huntington's disease. Neuroscience, 109(1), 81–88. https://doi.org/10.1016/S0306-4522(01)00409-2

Clifton, E. A. D., Perry, J. R. B., Imamura, F., Lotta, L. A., Brage, S., Forouhi, N. G., Griffin, S. J., Wareham, N. J., Ong, K. K., & Day, F. R. (2018). Genome-wide association study for risk taking propensity indicates shared pathways with body mass index. Communications Biology, 1(1). https://doi.org/10.1038/s42003-018-0042-6

Co, M., Hickey, S. L., Kulkarni, A., Harper, M., & Konopka, G. (2019). Cortical Foxp2 supports behavioral flexibility and developmental dopamine D1 receptor expression. BioRxiv, 624973. https://doi.org/10.1101/624973

Congdon, E., & Canli, T. (2005). The endophenotype of impulsivity: Reaching consilience through behavioral, genetic, and neuroimaging approaches. In Behavioral and Cognitive Neuroscience Reviews (Vol. 4, Issue 4, pp. 262–281). Behav Cogn Neurosci Rev. https://doi.org/10.1177/1534582305285980

Conneally, P. M. (1984). Huntington Disease: Genetics and Epidemiology. Am J Hum Genet, 36, 506–526.

Conner, J. M., Lauterborn, J. C., Yan, Q., Gall, C. M., & Varon, S. (1997). Distribution of Brain-Derived Neurotrophic Factor (BDNF) Protein and mRNA in the Normal Adult Rat CNS: Evidence for Anterograde Axonal Transport.

Coutinho, P., Pavlou, S., Bhatia, S., Chalmers, K. J., Kleinjan, D. A., & van Heyningen, V. (2011). Discovery and assessment of conserved Pax6 target genes and enhancers. Genome Research, 21(8), 1349–1359. https://doi.org/10.1101/GR.124115.111

Coyle, J. T., & Schwarcz, R. (1976). Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. Nature 1976 263:5574, 263(5574), 244–246. https://doi.org/10.1038/263244a0

Creus-Muncunill, J., Badillos-Rodríguez, R., Garcia-Forn, M., Masana, M., Garcia-Díaz Barriga, G., Guisado-Corcoll, A., Alberch, J., Malagelada, C., Delgado-García, J. M., Gruart, A., & Pérez-Navarro, E. (2019). Increased translation as a novel pathogenic mechanism in Huntington's disease. Brain, 142(10), 3158–3175. https://doi.org/10.1093/BRAIN/AWZ230

Crevier-Sorbo, G., Rymar, V. v., Crevier-Sorbo, R., & Sadikot, A. F. (2020). Thalamostriatal degeneration contributes to dystonia and cholinergic interneuron dysfunction in a mouse model of Huntington's disease. Acta Neuropathologica Communications 2020 8:1, 8(1), 1–19. https://doi.org/10.1186/S40478-020-0878-0

Cummings, D. M. (2006). Aberrant cortical synaptic plasticity and dopaminergic dysfunction in a mouse model of huntington's disease. Human Molecular Genetics, 15(19), 2856–2868. https://doi.org/10.1093/hmg/ddl224

Cummings, D. M., Milnerwood, A. J., Dallérac, G. M., Waights, V., Brown, J. Y., Vatsavayai, S. C., Hirst, M. C., & Murphy, K. P. S. J. (2006). Aberrant cortical synaptic plasticity and dopaminergic dysfunction in a mouse model of huntington's disease. Human Molecular Genetics, 15(19), 2856–2868. https://doi.org/10.1093/HMG/DDL224

Cummings, D. M., André, V.M., Uzgil, B.O., Gee, S.M., Fisher, Y.E., Cepeda, C., & Levine, M.S. (2009). Alterations in cortical excitation and inhibition in genetic mouse models of Huntington's disease. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 29(33), 10371–10386. https://doi.org/10.1523/JNEUROSCI.1592-09.2009

Dahoun, T., Trossbach, S. v, Brandon, N. J., Korth, C., & Howes, O. D. (2017). The impact of Disrupted-in-Schizophrenia 1 (DISC1) on the dopaminergic system: a systematic review. Translational Psychiatry 2017 7:1, 7(1), e1015–e1015. https://doi.org/10.1038/tp.2016.282

Dalbem, A., Silveira, C. V., Pedroso, M. F., Breda, R. V., Werne Baes, C. von, Bartmann, A. P., & da Costa, J. C. (2005). Altered distribution of striatal activity-dependent synaptic plasticity in the 3-nitropropionic acid model of Huntington's disease. Brain Research, 1047(2), 148–158. https://doi.org/10.1016/J.BRAINRES.2005.04.030

Dalby, M. A. (1969). Effect of Tetrabenazine on Extrapyramidal Movement Disorders. British Medical Journal, 2(5654), 422. https://doi.org/10.1136/BMJ.2.5654.422

Dallérac, G. M., Vatsavayai, S. C., Cummings, D. M., Milnerwood, A. J., Peddie, C. J., Evans, K. A., Walters, S. W., Rezaie, P., Hirst, M. C., & Murphy, K. P. S. J. (2011). Impaired long-term potentiation in the prefrontal cortex of Huntington's disease mouse models: Rescue by D1 dopamine receptor activation. Neurodegenerative Diseases, 8(4), 230–239. https://doi.org/10.1159/000322540

Dalley, J. W., & Robbins, T. W. (2017). Fractionating impulsivity: neuropsychiatric implications. Nature Reviews Neuroscience 2017 18:3, 18(3), 158–171. https://doi.org/10.1038/NRN.2017.8

Dark, C., Homman-Ludiye, J., & Bryson-Richardson, R. J. (2018). The role of ADHD associated genes in neurodevelopment. Developmental Biology, 438(2), 69–83. https://doi.org/10.1016/J.YDBIO.2018.03.023

Davies, S. W., Turmaine, M., Cozens, B. A., DiFiglia, M., Sharp, A. H., Ross, C. A., Scherzinger, E., Wanker, E. E., Mangiarini, L., & Bates, G. P. (1997). Formation of Neuronal Intranuclear Inclusions Underlies the Neurological Dysfunction in Mice Transgenic for the HD Mutation. Cell, 90(3), 537–548. https://doi.org/10.1016/S0092-8674(00)80513-9

Dawbarn, D., de Quidt, M. E., & Emson, P. C. (1985). Survival of basal ganglia neuropeptide Y-somatostatin neurones in Huntington's disease. Brain Research, 340(2), 251–260. https://doi.org/10.1016/0006-8993(85)90921-7

Day, N. F., Hobbs, T. G., Heston, J. B., & White, S. A. (2019). Beyond Critical Period Learning: Striatal FoxP2 Affects the Active Maintenance of Learned Vocalizations in Adulthood. ENeuro, 6(2), 71–90. https://doi.org/10.1523/ENEURO.0071-19.2019

Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Als, T. D., Agerbo, E., Baldursson, G., Belliveau, R., Bybjerg-Grauholm, J., Baekvad-Hansen, M., Hansen, C. S., Hauberg, M. E., Hollegaard, M. v, Howrigan, D. P., Huang, H., Maller, J. B., Martin, A. R., Martin, N. G., Moran, J., … Neale, B. M. (2019). ADHD Working Group of the Psychiatric Genomics Consortium

(PGC) 30 , Early Lifecourse & Genetic Epidemiology (EAGLE) Consortium 30 , 23andMe Research Team 30 , Ole A. Andreassen 31. Nature Genetics, 4(1), 63. https://doi.org/10.1038/s41588-018-0269-7

Deng, Wong, T., Bricker-Anthony, C., Deng, B., & Reiner, A. (2013). Loss of corticostriatal and thalamostriatal synaptic terminals precedes striatal projection neuron pathology in heterozygous Q140 Huntington's disease mice. Neurobiology of Disease, 60, 89–107. https://doi.org/10.1016/J.NBD.2013.08.009

Deng, Wong, T., Wan, J. Y., & Reiner, A. (2014). Differential loss of thalamostriatal and corticostriatal input to striatal projection neuron types prior to overt motor symptoms in the Q140 knock-in mouse model of Huntington's disease. Frontiers in Systems Neuroscience, 0(OCT), 198. https://doi.org/10.3389/FNSYS.2014.00198

Desplats, P. A., Kass, K. E., Gilmartin, T., Stanwood, G. D., Woodward, E. L., Head, S. R., Sutcliffe, J. G., & Thomas, E. A. (2006). Selective deficits in the expression of striatal-enriched mRNAs in Huntington's disease. Journal of Neurochemistry, 96(3), 743–757. https://doi.org/10.1111/j.1471-4159.2005.03588.x

Devanna, P., Middelbeek, J., & Vernes, S. C. (2014). FOXP2 drives neuronal differentiation by interacting with retinoic acid signaling pathways. Frontiers in Cellular Neuroscience, 0(SEP), 305. https://doi.org/10.3389/FNCEL.2014.00305

Díaz-Hernández, E., Contreras-López, R., Sánchez-Fuentes, A., Rodríguez-Sibrían, L., Ramírez-Jarquín, J. O., & Tecuapetla, F. (2018). The Thalamostriatal Projections Contribute to the Initiation and Execution of a Sequence of Movements. Neuron, 100(3), 739-752.e5. https://doi.org/10.1016/J.NEURON.2018.09.052

DiFiglia, M., Sapp, E., Chase, K., Schwarz, C., Meloni, A., Young, C., Martin, E., Vonsattel, J. P., Carraway, R., Reeves, S. A., Boyce, F. M., & Aronin, N. (1995). Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron, 14(5), 1075–1081. https://doi.org/10.1016/0896-6273(95)90346-1

DiFiglia, M., Sapp, E., Chase, K. O., Davies, S. W., Bates, G. P., Vonsattel, J. P., & Aronin, N. (1997). Aggregation of Huntingtin in Neuronal Intranuclear Inclusions and Dystrophic Neurites in Brain. Science, 277(5334). http://science.sciencemag.org/content/277/5334/1990.full

Ding, J., Peterson, J. D., & Surmeier, D. J. (2008). Corticostriatal and Thalamostriatal Synapses Have Distinctive Properties. Journal of Neuroscience, 28(25), 6483–6492. https://doi.org/10.1523/JNEUROSCI.0435-08.2008

Ding, J. B., Guzman, J. N., Peterson, J. D., Goldberg, J. A., & Surmeier, D. J. (2010). Thalamic gating of corticostriatal signaling by cholinergic interneurons. Neuron, 67(2), 294–307. https://doi.org/10.1016/J.NEURON.2010.06.017

Divac, I., Markowitsch, H. J., & Pritzel, M. (1978). Behavioral and anatomical consequences of small intrastriatal injections of kainic acid in the rat. Brain Research, 151(3), 523–532. https://doi.org/10.1016/0006-8993(78)91084-3

Dodds, L., Chen, J., Berggren, K., & Fox, J. (2014). Characterization of Striatal Neuronal Loss and Atrophy in the R6/2 Mouse Model of Huntington's Disease. PLoS Currents, 6(JAN). https://doi.org/10.1371/CURRENTS.HD.48727B68B39B82D5FE350F753984BCF9

Dogan, I., Eickhoff, C. R., Fox, P. T., Laird, A. R., Schulz, J. B., Eickhoff, S. B., & Reetz, K. (2015). Functional connectivity modeling of consistent cortico-striatal degeneration in Huntington's disease. NeuroImage: Clinical, 7, 640–652. https://doi.org/10.1016/J.NICL.2015.02.018

REFERENCES

Dom, R., Malfroid, M., & Baro, F. (1976). Neuropathology of Huntington's chorea: Studies of the ventrobasal complex of the thalamus. Neurology, 26(1), 64–68. https://doi.org/10.1212/wnl.26.1.64

Dominguez, M. H., Ayoub, A. E., & Rakic, P. (2013). POU-III Transcription Factors (Brn1, Brn2, and Oct6) Influence Neurogenesis, Molecular Identity, and Migratory Destination of Upper-Layer Cells of the Cerebral Cortex. Cerebral Cortex, 23(11), 2632–2643. https://doi.org/10.1093/CERCOR/BHS252

Donzis, E. J., Estrada-Sánchez A.M., Indersmitten, Oikonomou, K., Tran, C. H., Wang, C., Latifi, S., Golshani, P., Cepeda, C., & Levine, M. S. (2020). Cortical Network Dynamics Is Altered in Mouse Models of Huntington's Disease. Cerebral Cortex (New York, N.Y. : 1991), 30(4), 2372–2388. https://doi.org/10.1093/CERCOR/BHZ245

Dragatsis, I., Goldowitz, D., del Mar, N., Deng, Y. P., Meade, C. A., Liu, L., Sun, Z., Dietrich, P., Yue, J., & Reiner, A. (2009). CAG repeat lengths ≥ 335 attenuate the phenotype in the R6/2 Huntington's disease transgenic mouse. Neurobiology of Disease, 33(3), 315–330. https://doi.org/10.1016/J.NBD.2008.10.009

Druart, M., Groszer, M., & Magueresse, C. le. (2020). An Etiological Foxp2 Mutation Impairs Neuronal Gain in Layer VI Cortico-Thalamic Cells through Increased GABAB/GIRK Signaling. The Journal of Neuroscience, 40(44), 8543. https://doi.org/10.1523/JNEUROSCI.2615-19.2020

Du, Z., Tertrais, M., Courtand, G., Leste-Lasserre, T., Cardoit, L., Masmejean, F., Halgand, C., Cho, Y. H., & Garret, M. (2017). Differential Alteration in Expression of Striatal GABAAR Subunits in Mouse Models of Huntington's Disease. Frontiers in Molecular Neuroscience, 0, 198. https://doi.org/10.3389/FNMOL.2017.00198

Duan, W., Guo, Z., Jiang, H., Ware, M., Li, X. J., & Mattson, M. P. (2003). Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proceedings of the National Academy of Sciences of the United States of America, 100(5), 2911–2916. https://doi.org/10.1073/PNAS.0536856100

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(1), 377–384. https://doi.org/10.1016/J.NICL.2013.03.001

Dunah, A. W., Jeong, H., Griffin, A., Kim, Y.-M., Standaert, D. G., Hersch, S. M., Mouradian, M. M., Young, A. B., Tanese, N., & Krainc, D. (2002). Sp1 and TAFII130 Transcriptional Activity Disrupted in Early Huntington's Disease. Science, 296(5576), 2238–2243. https://doi.org/10.1126/SCIENCE.1072613

Duyao, M., Lazzarini, A., Falek, A., Koroshetz8, W., Sax2, D., Bird, E., Vonsattel1, J., Bonilla, E., Alvir, J., Bickham Conde', J., Cha, J.-H., Dure, L., Gomez, F., Ramos, M., Sanchez-Ramos, J., Snodgrass, S., de Young, M., Wexler2, N., Moscowitz, C., … Macdonald, & M. (1993). Trinucleotide repeat length instability and age of onset in Huntington's disease. http://www.nature.com/naturegenetics

Duyao, M. P., Auerbach, A. B., Ryan, A., Persichetti, F., Barnes, G. T., McNeil, S. M., Ge, P., Vonsattel, J. P., Gusella, J. F., Joyner, A. L., & MacDonald, M. E. (1995). Inactivation of the mouse huntington's disease gene homolog Hdh. Science, 269(5222), 407–410. https://doi.org/10.1126/science.7618107

Ebisu, H., Iwai-Takekoshi, L., Fujita-Jimbo, E., Momoi, T., & Kawasaki, H. (2017). Foxp2 Regulates Identities and Projection Patterns of Thalamic Nuclei During Development. Cerebral Cortex, 27(7), 3648–3659. https://doi.org/10.1093/CERCOR/BHW187

Eddy, C. M., Parkinson, E. G., & Rickards, H. E. (2016). Changes in mental state and behaviour in Huntington's disease. In The Lancet Psychiatry (Vol. 3, Issue 11, pp. 1079–1086). Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(16)30144-4

Edwardson, J. M., Wang, C.-T., Gong, B., Wyttenbach, A., Bai, J., Jackson, M. B., Chapman, E. R., & Morton, A. J. (2003). Expression of Mutant Huntingtin Blocks Exocytosis in PC12 Cells by Depletion of Complexin II *. Journal of Biological Chemistry, 278(33), 30849–30853. https://doi.org/10.1074/JBC.M304615200

El-Boustani, S., Sermet, B. S., Foustoukos, G., Oram, T. B., Yizhar, O., & Petersen, C. C. H. (2020). Anatomically and functionally distinct thalamocortical inputs to primary and secondary mouse whisker somatosensory cortices. Nature Communications 2020 11:1, 11(1), 1–12. https://doi.org/10.1038/s41467-020-17087-7

Elena. (2018). Utah Medicaid Pharmacy and Therapeutics Committee Drug Class Review Vesicular Monoamine Transporter 2 Inhibitors and Anticholinergic Agents for Movement Disorders.

Enard, W., Gehre, S., Hammerschmidt, K., Hölter, S. M., Blass, T., Somel, M., Brückner, M. K., Schreiweis, C., Winter, C., Sohr, R., Becker, L., Wiebe, V., Nickel, B., Giger, T., Müller, U., Groszer, M., Adler, T., Aguilar, A., Bolle, I., … Pääbo, S. (2009). A Humanized Version of Foxp2 Affects Cortico-Basal Ganglia Circuits in Mice. Cell, 137(5), 961–971. https://doi.org/10.1016/j.cell.2009.03.041

Engmann, O., Giralt, A., Gervasi, N., Marion-Poll, L., Gasmi, L., Filhol, O., Picciotto, M. R., Gilligan, D., Greengard, P., Nairn, A. C., Hervé, D., & Girault, J.-A. (2015). DARPP-32 interaction with adducin may mediate rapid environmental effects on striatal neurons. Nature Communications 2015 6:1, 6(1), 1–14. https://doi.org/10.1038/ncomms10099

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., & Group, the P.-H. I. and C. of the H. S. (2016). Longitudinal Psychiatric Symptoms Progress in Prodromal Huntington Disease: a Decade of Data. The American Journal of Psychiatry, 173(2), 184. https://doi.org/10.1176/APPI.AJP.2015.14121551

Estrada-Sánchez, A. M., Montiel, T., Segovia, J., & Massieu, L. (2009). Glutamate toxicity in the striatum of the R6/2 Huntington's disease transgenic mice is age-dependent and correlates with decreased levels of glutamate transporters. Neurobiology of Disease, 34(1), 78–86. https://doi.org/10.1016/J.NBD.2008.12.017

Estrada-Sánchez, A. M., & Rebec, G. v. (2012). Corticostriatal dysfunction and glutamate transporter 1 (GLT1) in Huntington's disease: Interactions between neurons and astrocytes. Basal Ganglia, 2(2), 57–66. https://doi.org/10.1016/J.BAGA.2012.04.029

Etxeberria-Rekalde, E., Alzola-Aldamizetxebarria, S., Flunkert, S., Hable, I., Daurer, M., Neddens, J., & Hutter-Paier, B. (2021). Quantification of Huntington's Disease Related Markers in the R6/2 Mouse Model. Frontiers in Molecular Neuroscience, 0, 255. https://doi.org/10.3389/FNMOL.2020.617229

Fan, M. M. Y., & Raymond, L. A. (2007). N-Methyl-d-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. Progress in Neurobiology, 81(5–6), 272–293. https://doi.org/10.1016/J.PNEUROBIO.2006.11.003

Faraone, S. v., & Larsson, H. (2018). Genetics of attention deficit hyperactivity disorder. Molecular Psychiatry 2018 24:4, 24(4), 562–575. https://doi.org/10.1038/s41380-018-0070-0

Feigin, A., Ghilardi, M. F., Huang, C., Ma, Y., Carbon, M., Guttman, M., Paulsen, J. S., Ghez, C. P., & Eidelberg, D. (2006). Preclinical Huntington's disease: Compensatory brain responses during learning. Annals of Neurology, 59(1), 53–59. https://doi.org/10.1002/ANA.20684

Feigin, A., Tang, C., Ma, Y., Mattis, P., Zgaljardic, D., Guttman, M., Paulsen, J. S., Dhawan, V., & Eidelberg, D. (2007). Thalamic metabolism and symptom onset in preclinical Huntington's disease. Brain, 130(11), 2858–2867. https://doi.org/10.1093/BRAIN/AWM217

Fenlon, L. R., Liu, S., Gobius, I., Kurniawan, N. D., Murphy, S., Moldrich, R. X., & Richards, L. J. (2015). Formation of functional areas in the cerebral cortex is disrupted in a mouse model of autism spectrum disorder. Neural Development, 10(1). https://doi.org/10.1186/S13064-015-0033-Y

Ferland, R. J., Cherry, T. J., Preware, P. O., Morrisey, E. E., & Walsh, C. A. (2003). Characterization of Foxp2 and Foxp1 mRNA and protein in the developing and mature brain. Journal of Comparative Neurology, 460(2), 266–279. https://doi.org/10.1002/cne.10654

Fernández-García, S., Conde-Berriozabal, S., García-García, E., Gort-Paniello, C., Bernal-Casas, D., Barriga, G. G. D., López-Gil, J., Muñoz-Moreno, E., Soria, G., Campa, L., Artigas, F., Rodríguez, M. J., Alberch, J., & Masana, M. (2020). M2 cortex-dorsolateral striatum stimulation reverses motor symptoms and synaptic deficits in huntington's disease. ELife, 9, 1–24. https://doi.org/10.7554/ELIFE.57017

Ferrante, R. J. (2009). Mouse models of Huntington's disease and methodological considerations for therapeutic trials. Biochimica et Biophysica Acta - Molecular Basis of Disease, 1792(6), 506–520. https://doi.org/10.1016/J.BBADIS.2009.04.001

Ferrante, R. J., Flint Beal, M., Kowall, N. W., Richardson, E. P., & Martin, J. B. (1987). Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease. Brain Research, 411(1), 162–166. https://doi.org/10.1016/0006-8993(87)90694-9

Ferrante, R., Kowall, N., & Richardson, E. (1991). Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry. Journal of Neuroscience, 11(12). http://www.jneurosci.org/content/11/12/3877.long

Feuk, L., Kalervo, A., Lipsanen-Nyman, M., Skaug, J., Nakabayashi, K., Finucane, B., Hartung, D., Innes, M., Kerem, B., Nowaczyk, M. J., Rivlin, J., Roberts, W., Senman, L., Summers, A., Szatmari, P., Wong, V., Vincent, J. B., Zeesman, S., Osborne, L. R., … Hannula-Jouppi, K. (2006). Absence of a paternally inherited FOXP2 gene in developmental verbal dyspraxia. American Journal of Human Genetics, 79(5), 965–972. https://doi.org/10.1086/508902

French, C. A., Jin, X., Campbell, T. G., Gerfen, E., Groszer, M., Fisher, S. E., & Costa, R. M. (2012). An aetiological Foxp2 mutation causes aberrant striatal activity and alters plasticity during skill learning. Molecular Psychiatry, 17(11), 1077–1085. https://doi.org/10.1038/MP.2011.105

French, C. A., Vinueza Veloz, M. F., Zhou, K., Peter, S., Fisher, S. E., Costa, R. M., & de Zeeuw, C. I. (2018). Differential effects of Foxp2 disruption in distinct motor circuits. Molecular Psychiatry 2018 24:3, 24(3), 447–462. https://doi.org/10.1038/s41380-018-0199-x

Friedman, J. I., Vrijenhoek, T., Markx, S., Janssen, I. M., van der Vliet, W. A., Faas, B. H. W., Knoers, N. v, Cahn, W., Kahn, R. S., Edelmann, L., Davis, K. L., Silverman, J. M., Brunner, H. G., van Kessel, A. G., Wijmenga, C., Ophoff, R. A., & Veltman, J. A. (2007). CNTNAP2 gene dosage

variation is associated with schizophrenia and epilepsy. Molecular Psychiatry 2008 13:3, 13(3), 261–266. https://doi.org/10.1038/sj.mp.4002049

Gallardo-Orihuela, A., Hervás-Corpión, I., Hierro-Bujalance, C., Sanchez-Sotano, D., Jiménez-Gómez, G., Mora-López, F., Campos-Caro, A., Garcia-Alloza, M., & Valor, L. M. (2019). Transcriptional correlates of the pathological phenotype in a Huntington's disease mouse model. Scientific Reports 2019 9:1, 9(1), 1–12. https://doi.org/10.1038/s41598-019-55177-9

Galvan, L., André, V. M., Wang, E. A., Cepeda, C., & Levine, M. S. (2012). Functional Differences Between Direct and Indirect Striatal Output Pathways in Huntington's Disease. Journal of Huntington's Disease, 1(1), 17. https://doi.org/10.3233/JHD-2012-120009

Galvez, V., Fernandez-Ruiz, J., Bayliss, L., Ochoa-Morales, A., Hernandez-Castillo, C. R., DIáz, R., & Campos-Romo, A. (2017). Early Huntington's Disease: Impulse control deficits but correct judgment regarding risky situations. Journal of Huntington's Disease, 6(1), 73–78. https://doi.org/10.3233/JHD-160223

Gao, R., Chakraborty, A., Geater, C., Pradhan, S., Gordon, K. L., Snowden, J., Yuan, S., Dickey, A. S., Choudhary, S., Ashizawa, T., Ellerby, L. M., la Spada, A. R., Thompson, L. M., Hazra, T. K., & Sarkar, P. S. (2019). Mutant huntingtin impairs PNKP and ATXN3, disrupting DNA repair and transcription. ELife, 8. https://doi.org/10.7554/ELIFE.42988

Garcia-Calero, E., Botella-Lopez, A., Bahamonde, O., Perez-Balaguer, A., & Martinez, S. (2016). FoxP2 protein levels regulate cell morphology changes and migration patterns in the vertebrate developing telencephalon. Brain Structure and Function, 221(6), 2905–2917. https://doi.org/10.1007/S00429-015-1079-7

Garrett, M. C., & Soares-da-Silva, P. (1992). Increased Cerebrospinal Fluid Dopamine and 3,4-Dihydroxyphenylacetic Acid Levels in Huntington's Disease: Evidence for an Overactive Dopaminergic Brain Transmission. Journal of Neurochemistry, 58(1), 101–106. https://doi.org/10.1111/J.1471-4159.1992.TB09283.X

Gatto, R., & Weissmann, C. (2022). Preliminary examination of early neuroconnectivity features in the R6/1 mouse model of Huntington's disease by ultra-high field diffusion MRI. Neural Regeneration Research, 17(5), 983. https://doi.org/10.4103/1673-5374.324831

Gauthier, L. R., Charrin, B. C., Borrell-Pagès, M., Dompierre, J. P., Rangone, H., Cordelières, F. P., de Mey, J., MacDonald, M. E., Leßmann, V., Humbert, S., & Saudou, F. (2004). Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell, 118(1), 127–138. https://doi.org/10.1016/j.cell.2004.06.018

Geppert, M., Bolshakov, V. Y., Siegelbaum, S. A., Takei, K., de Camilli, P., Hammer, R. E., & Südhof, T. C. (1994). The role of Rab3A in neurotransmitter release. Nature 1994 369:6480, 369(6480), 493–497. https://doi.org/10.1038/369493a0

Gertler, T. S., Chan, C. S., & Surmeier, D. J. (2008). Dichotomous anatomical properties of adult striatal medium spiny neurons. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 28(43), 10814–10824. https://doi.org/10.1523/JNEUROSCI.2660-08.2008

Ghiglieri, V., Campanelli, F., Marino, G., Natale, G., Picconi, B., & Calabresi, P. (2019). Corticostriatal synaptic plasticity alterations in the R6/1 transgenic mouse model of Huntington's disease. Journal of Neuroscience Research, 97(12), 1655–1664. https://doi.org/10.1002/JNR.24521

Ghosh, R., & Tabrizi, S. J. (2018). Clinical Features of Huntington's Disease. Advances in Experimental Medicine and Biology, 1049, 1–28. https://doi.org/10.1007/978-3-319-71779-1_1

REFERENCES

Giampà, C., Middei, S., Patassini, S., Borreca, A., Marullo, F., Laurenti, D., Bernardi, G., Ammassari-Teule, M., & Fusco, F. R. (2009). Phosphodiesterase type IV inhibition prevents sequestration of CREB binding protein, protects striatal parvalbumin interneurons and rescues motor deficits in the R6/2 mouse model of Huntington's disease. European Journal of Neuroscience, 29(5), 902–910. https://doi.org/10.1111/j.1460-9568.2009.06649.x

Ginovart, N., Lundin, A., Farde, L., Halldin, C., Bäckman, L., Swahn, C. G., Pauli, S., & Sedvall, G. (1997). PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease. Brain, 120(3), 503–514. https://doi.org/10.1093/BRAIN/120.3.503

Giralt, A., Friedman, H. C., Caneda-Ferrón, B., Urbán, N., Moreno, E., Rubio, N., Blanco, J., Peterson, A., Canals, J. M., & Alberch, J. (2010). BDNF regulation under GFAP promoter provides engineered astrocytes as a new approach for long-term protection in Huntington's disease. Gene Therapy, 17(10), 1294–1308. https://doi.org/10.1038/gt.2010.71

Giralt, A., Carretón, O., Lao-Peregrin, C., Martín, E. D., & Alberch, J. (2011). Conditional BDNF release under pathological conditions improves Huntington's disease pathology by delaying neuronal dysfunction. Molecular Neurodegeneration 2011 6:1, 6(1), 1–16. https://doi.org/10.1186/1750-1326-6-71

Giralt, A., Saavedra, A., Carretón, O., Xifró, X., Alberch, J., & Pérez-navarro, E. (2011). Increased PKA signaling disrupts recognition memory and spatial memory: Role in Huntington's disease. Human Molecular Genetics, 20(21), 4232–4247. https://doi.org/10.1093/hmg/ddr351

Giralt, A., Brito, V., Chevy, Q., Simonnet, C., Otsu, Y., Cifuentes-Díaz, C., Pins, B. de, Coura, R., Alberch, J., Ginés, S., Poncer, J.-C., & Girault, J.-A. (2017). Pyk2 modulates hippocampal excitatory synapses and contributes to cognitive deficits in a Huntington's disease model. Nature Communications 2017 8:1, 8(1), 1–16. https://doi.org/10.1038/ncomms15592

Ghosh, R. & Tabrizi S. J. (2018). Huntington disease. Handbook of Clinical Neurology, 147, 255–278. https://doi.org/10.1016/B978-0-444-63233-3.00017-8

Gladding, C. M., Sepers, M. D., Xu, J., Zhang, L. Y. J., Milnerwood, A. J., Lombroso, P. J., & Raymond, L. A. (2012). Calpain and STriatal-Enriched protein tyrosine Phosphatase (STEP) activation contribute to extrasynaptic NMDA receptor localization in a Huntington's disease mouse model. Human Molecular Genetics, 21(17), 3739. https://doi.org/10.1093/HMG/DDS154

Glenn, A. L., & Yang, Y. (2012). The potential role of the striatum in antisocial behavior and psychopathy. Biological Psychiatry, 72(10), 817–822. https://doi.org/10.1016/J.BIOPSYCH.2012.04.027

Goh, A. M., Wibawa, P., Loi, S. M., Walterfang, M., Velakoulis, D., & Looi, J. C. (2018). Huntington's disease: Neuropsychiatric manifestations of Huntington's disease: Https://Doi.Org/10.1177/1039856218791036, 26(4), 366–375. https://doi.org/10.1177/1039856218791036

Goldberg, Y. P., Kremer, B., Andrew, S. E., Theilmann, J., Graham, R. K., Squitieri, F., Telenius, H., Adam, S., Sajoo, A., Starr, E., Heiberg, A., Wolff, G., & Hayden, M. R. (1993). Molecular analysis of new mutations for Huntington's disease: Intermediate alleles and sex of origin effects. Nature Genetics, 5(2), 174–179. https://doi.org/10.1038/ng1093-174

Golson, M. L., & Kaestner, K. H. (2016). Fox transcription factors: from development to disease. Development (Cambridge, England), 143(24), 4558. https://doi.org/10.1242/DEV.112672

Gomez-Tortosa, E., MacDonald, ME., & Friend, JC. (2001). Quantitative neuropathological changes in presymptomatic Huntington's disease. Annals of Neurology, 49(1), 29–34. https://doi.org/10.1002/1531-8249(200101)49:1<29::aid-ana7>3.0.co

Gopnik, M., & Crago, M. B. (1991). Familial aggregation of a developmental language disorder. Cognition, 39(1), 1–50. https://doi.org/10.1016/0010-0277(91)90058-C

Graveland, G., Williams, R., & DiFiglia, M. (1985). Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. Science, 227(4688). http://science.sciencemag.org/content/227/4688/770/tab-pdf

Gray, M., Shirasaki, D. I., Cepeda, C., André, V. M., Wilburn, B., Lu, X. H., Tao, J., Yamazaki, I., Li, S. H., Sun, Y. E., Li, X. J., Levine, M. S., & Yang, X. W. (2008). Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. Journal of Neuroscience, 28(24), 6182–6195. https://doi.org/10.1523/JNEUROSCI.0857-08.2008

Groszer, M., Keays, D. A., Deacon, R. M. J., de Bono, J. P., Prasad-Mulcare, S., Gaub, S., Baum, M. G., French, C. A., Nicod, J., Coventry, J. A., Enard, W., Fray, M., Brown, S. D. M., Nolan, P. M., Pääbo, S., Channon, K. M., Costa, R. M., Eilers, J., Ehret, G., … Fisher, S. E. (2008). Impaired Synaptic Plasticity and Motor Learning in Mice with a Point Mutation Implicated in Human Speech Deficits. Current Biology, 18(5), 354–362. https://doi.org/10.1016/j.cub.2008.01.060

Grote, H. E., Bull, N. D., Howard, M. L., Dellen, A. van, Blakemore, C., Bartlett, P. F., & Hannan, A. J. (2005). Cognitive disorders and neurogenesis deficits in Huntington's disease mice are rescued by fluoxetine. European Journal of Neuroscience, 22(8), 2081–2088. https://doi.org/10.1111/J.1460-9568.2005.04365.X

Guay, D. R. P. (2010). Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinetic movement disorders. In American Journal Geriatric Pharmacotherapy (Vol. 8, Issue 4, pp. 331–373). Am J Geriatr Pharmacother. https://doi.org/10.1016/j.amjopharm.2010.08.006

Guiretti, D., Sempere, A., Lopez-Atalaya, J. P., Ferrer-Montiel, A., Barco, A., & Valor, L. M. (2016). Specific promoter deacetylation of histone H3 is conserved across mouse models of Huntington's disease in the absence of bulk changes. Neurobiology of Disease, 89, 190–201. https://doi.org/10.1016/j.nbd.2016.02.004

Gunaydin, L. A., & Kreitzer, A. C. (2016). Cortico–Basal Ganglia Circuit Function in Psychiatric Disease. Http://Dx.Doi.Org.Sire.Ub.Edu/10.1146/Annurev-Physiol-021115-105355, 78, 327–350. https://doi.org/10.1146/ANNUREV-PHYSIOL-021115-105355

Guo, K., Yamawaki, N., Barrett, J. M., Tapies, M., & Shepherd, G. M. G. (2020). Cortico-Thalamo-Cortical Circuits of Mouse Forelimb S1 Are Organized Primarily as Recurrent Loops. Journal of Neuroscience, 40(14), 2849–2858. https://doi.org/10.1523/JNEUROSCI.2277-19.2020

Gusella, J. F., Wexler, N. S., Conneally, P. M., Naylor, S. L., Anderson, M. A., Tanzi, R. E., Watkins, P. C., Ottina, K., Wallace, M. R., Sakaguchi, A. Y., Young, A. B., Shoulson, I., Bonilla, E., & Martin, J. B. (1983). A polymorphic DNA marker genetically linked to Huntington's disease. Nature, 306(5940), 234–238. https://doi.org/10.1038/306234a0

Gutekunst, C. A., Levey, A. I., Heilman, C. J., Whaley, W. L., Yi, H., Nash, N. R., Rees, H. D., Madden, J. J., & Hersch, S. M. (1995). Identification and localization of huntingtin in brain and human lymphoblastoid cell lines with anti-fusion protein antibodies. Proceedings of the

National Academy of Sciences of the United States of America, 92(19), 8710. https://doi.org/10.1073/PNAS.92.19.8710

Gutekunst, C.-A., Li, S.-H., Yi, H., Mulroy, J. S., Kuemmerle, S., Jones, R., Rye, D., Ferrante, R. J., Hersch, S. M., & Li, X.-J. (1999). Nuclear and Neuropil Aggregates in Huntington's Disease: Relationship to Neuropathology. Journal of Neuroscience, 19(7), 2522–2534. https://doi.org/10.1523/JNEUROSCI.19-07-02522.1999

Hachigian, L. J., Carmona, V., Fenster, R. J., Kulicke, R., Heilbut, A., Sittler, A., Pereira de Almeida, L., Mesirov, J. P., Gao, F., Kolaczyk, E. D., & Heiman, M. (2017). Control of Huntington's Disease-Associated Phenotypes by the Striatum-Enriched Transcription Factor Foxp2. Cell Reports, 21(10), 2688–2695. https://doi.org/10.1016/j.celrep.2017.11.018

Haesler, S., Wada, K., Nshdejan, A., Morrisey, E. E., Lints, T., Jarvis, E. D., & Scharff, C. (2004). FoxP2 Expression in Avian Vocal Learners and Non-Learners. Journal of Neuroscience, 24(13), 3164–3175. https://doi.org/10.1523/JNEUROSCI.4369-03.2004

Hahn, T., Heinzel, S., Dresler, T., Plichta, M. M., Renner, T. J., Markulin, F., Jakob, P. M., Lesch, K. P., & Fallgatter, A. J. (2011). Association between reward-related activation in the ventral striatum and trait reward sensitivity is moderated by dopamine transporter genotype. Human Brain Mapping, 32(10), 1557–1565. https://doi.org/10.1002/hbm.21127

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 and Psychiatry, 74(1), 120–122. https://doi.org/10.1136/jnnp.74.1.120

Hansson, O., Guatteo, E., Mercuri, N. B., Bernardi, G., Li, X.-J., Castilho, R. F., & Brundin, P. (2001). Resistance to NMDA toxicity correlates with appearance of nuclear inclusions, behavioural deficits and changes in calcium homeostasis in mice transgenic for exon 1 of the huntington gene. European Journal of Neuroscience, 14(9), 1492–1504. https://doi.org/10.1046/J.0953-816X.2001.01767.X

Harrington, D. L., Rubinov, M., Durgerian, S., Mourany, L., Reece, C., Koenig, K., Bullmore, E., Long, J. D., Paulsen, J. S., & Rao, S. M. (2015). Network topology and functional connectivity disturbances precede the onset of Huntington's disease. Brain, 138(8), 2332–2346. https://doi.org/10.1093/BRAIN/AWV145

Harris, G. J., Aylward, E. H., Peyser, C. E., Pearlson, G. D., Brandt, J., Roberts-Twillie, J. v., Barta, P. E., & Folstein, S. E. (1996). Single photon emission computed tomographic blood flow and magnetic resonance volume imaging of basal ganglia in Huntington's disease. Archives of Neurology, 53(4), 316–324. https://doi.org/10.1001/ARCHNEUR.1996.00550040044013

Harris, K. L., Armstrong, M., Swain, R., Erzinclioglu, S., Das, T., Burgess, N., Barker, R. A., & Mason, S. L. (2019). Huntington's disease patients display progressive deficits in hippocampal-dependent cognition during a task of spatial memory. Cortex, 119, 417–427. https://doi.org/10.1016/J.CORTEX.2019.07.014

Harrison, D. J., Busse, M., Openshaw, R., Rosser, A. E., Dunnett, S. B., & Brooks, S. P. (2013). Exercise attenuates neuropathology and has greater benefit on cognitive than motor deficits in the R6/1 Huntington's disease mouse model. Experimental Neurology, 248, 457–469. https://doi.org/10.1016/J.EXPNEUROL.2013.07.014

Hassel, B., Tessler, S., Faull, R., & Emson, P. C. (2008). Glutamate uptake is reduced in prefrontal cortex in Huntington's disease. Neurochemical Research, 33(2), 232–237. https://doi.org/10.1007/S11064-007-9463-1

Hebb, M. O., Denovanwright, E. M., & Robertson, H. A. (1999). Expression of the Huntington's disease gene is regulated in astrocytes in the arcuate nucleus of the hypothalamus of postpartum rats. The FASEB Journal, 13(9), 1099–1106. https://doi.org/10.1096/fasebj.13.9.1099

Helder, D. I., Kaptein, A. A., van Kempen, G. M. J., van Houwelingen, J. C., & Roos, R. A. C. (2001). Impact of huntington's disease on quality of life. Movement Disorders, 16(2), 325–330. https://doi.org/10.1002/mds.1056

Hemachandra Reddy, P., Williams, M., Charles, V., Garrett, L., Pike-Buchanan, L., Whetsell, W. O., Miller, G., & Tagle, D. A. (1998). Behavioural abnormalities and selective neuronal loss in HD transgenic mice expressing mutated full-length HD cDNA. Nature Genetics, 20(2), 198–202. https://doi.org/10.1038/2510

Heng, M. Y., Detloff, P.J., Wang, P.L., Tsien, J. Z., & Albin, R. L. (2009). In vivo evidence for NMDA receptor-mediated excitotoxicity in a murine genetic model of Huntington disease. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 29(10), 3200–3205. https://doi.org/10.1523/JNEUROSCI.5599-08.2009

Henley, S. M. D., Wild, E. J., Hobbs, N. Z., Frost, C., MacManus, D. G., Barker, R. A., Fox, N. C., & Tabrizi, S. J. (2009). Whole-brain atrophy as a measure of progression in premanifest and early Huntington's disease. Movement Disorders, 24(6), 932–936. https://doi.org/10.1002/mds.22485

Hernández, I. H., Torres-Peraza, J., Santos-Galindo, M., Ramos-Morón, E., Fernández-Fernández, M. R., Pérez-Álvarez, M. J., Miranda-Vizuete, A., & Lucas, J. J. (2017). The neuroprotective transcription factor ATF5 is decreased and sequestered into polyglutamine inclusions in Huntington's disease. Acta Neuropathologica, 134(6), 839–850. https://doi.org/10.1007/S00401-017-1770-2

Hernandez, J., Shahani, N., Swarnkar, S., & Subramaniam, S. (2021). Rhes Deletion Prevents Age-Dependent Selective Motor Deficits and Reduces Phosphorylation of S6K in Huntington Disease Hdh150Q(CAG) Knock-In Mice. BioRxiv, 2021.06.16.448681. https://doi.org/10.1101/2021.06.16.448681

Herrero, M. J., Wang, L., Hernandez-Pineda, D., Banerjee, P., Matos, H. Y., Goodrich, M., Panigrahi, A., Smith, N. A., & Corbin, J. G. (2021). Sex-Specific Social Behavior and Amygdala Proteomic Deficits in Foxp2+/− Mutant Mice. Frontiers in Behavioral Neuroscience, 15. https://doi.org/10.3389/FNBEH.2021.706079

Heston, J. B., & White, S. A. (2015). Behavior-linked foxP2 regulation enables zebra finch vocal learning. Journal of Neuroscience, 35(7), 2885–2894. https://doi.org/10.1523/JNEUROSCI.3715-14.2015

Hevner, R. F., Shi, L., Justice, N., Hsueh, Y. P., Sheng, M., Smiga, S., Bulfone, A., Goffinet, A. M., Campagnoni, A. T., & Rubenstein, J. L. R. (2001). Tbr1 Regulates Differentiation of the Preplate and Layer 6. Neuron, 29(2), 353–366. https://doi.org/10.1016/S0896-6273(01)00211-2

Hickey, M. A., Gallant, K., Gross, G. G., Levine, M. S., & Chesselet, M. F. (2005). Early behavioral deficits in R6/2 mice suitable for use in preclinical drug testing. Neurobiology of Disease, 20(1), 1–11. https://doi.org/10.1016/J.NBD.2005.01.024

Hickey, M. A., Reynolds, G. P., & Morton, A. J. (2002). The role of dopamine in motor symptoms in the R6/2 transgenic mouse model of Huntington's disease. Journal of Neurochemistry, 81(1), 46–59. https://doi.org/10.1046/J.1471-4159.2002.00804.X

Hickey, M. A., Kosmalska, A., Enayati, J., Cohen, R., Zeitlin, S., Levine, M. S., & Chesselet, M. F. (2008). Extensive early motor and non-motor behavioral deficits are followed by striatal

neuronal loss in knock-in Huntington's disease mice. Neuroscience, 157(1), 280–295. https://doi.org/10.1016/J.NEUROSCIENCE.2008.08.041

Hintiryan, H., Foster, N. N., Bowman, I., Bay, M., Song, M. Y., Gou, L., Yamashita, S., Bienkowski, M. S., Zingg, B., Zhu, M., Yang, X. W., Shih, J. C., Toga, A. W., & Dong, H.-W. (2016). The mouse cortico-striatal projectome. Nature Neuroscience 2016 19:8, 19(8), 1100–1114. https://doi.org/10.1038/NN.4332

Ho, A. K., Gilbert, A. S., Mason, S. L., Goodman, A. O., & Barker, R. A. (2009). Health-related quality of life in Huntington's disease: Which factors matter most? Movement Disorders, 24(4), 574–578. https://doi.org/10.1002/mds.22412

Hodgkinson, C. A., Goldman, D., Jaeger, J., Persaud, S., Kane, J. M., Lipsky, R. H., & Malhotra, A. K. (2004). Disrupted in Schizophrenia 1 (DISC1): Association with Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder. The American Journal of Human Genetics, 75(5), 862–872. https://doi.org/10.1086/425586

Hodgson, J. G., Agopyan, N., Gutekunst, C. A., Leavitt, B. R., Lepiane, F., Singaraja, R., Smith, D. J., Bissada, N., McCutcheon, K., Nasir, J., Jamot, L., Xiao-Jiang, L., Stevens, M. E., Rosemond, E., Roder, J. C., Phillips, A. G., Rubin, E. M., Hersch, S. M., & Hayden, M. R. (1999). A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. Neuron, 23(1), 181–192. https://doi.org/10.1016/S0896-6273(00)80764-3

Hoffner, G., Kahlem, P., & Djian, P. (2002). Perinuclear localization of huntingtin as a consequence of its binding to microtubules through an interaction with β-tubulin: Relevance to Huntington's disease. Journal of Cell Science, 115(5), 941–948. https://doi.org/10.1242/JCS.115.5.941

Hölter, S. M., & Glasl, L. (2011). High-throughput mouse phenotyping. Neuromethods, 61, 109–133. https://doi.org/10.1007/978-1-61779-298-4_7

Hölter, S. M., Stromberg, M., Kovalenko, M., Garrett, L., Glasl, L., Lopez, E., Guide, J., Götz, A., Hans, W., Becker, L., Rathkolb, B., Rozman, J., Schrewed, A., Klingenspor, M., Klopstock, T., Schulz, H., Wolf, E., Wursta, W., Gillis, T., … Wheeler, V. C. (2013). A Broad Phenotypic Screen Identifies Novel Phenotypes Driven by a Single Mutant Allele in Huntington's Disease CAG Knock-In Mice. PLoS ONE, 8(11). https://doi.org/10.1371/JOURNAL.PONE.0080923

Hong, S. L., Cossyleon, D., Hussain, W. A., Walker, L. J., Barton, S. J., & Rebec, G. v. (2012). Dysfunctional Behavioral Modulation of Corticostriatal Communication in the R6/2 Mouse Model of Huntington's Disease. PLoS ONE, 7(10). https://doi.org/10.1371/JOURNAL.PONE.0047026

Hubers, A. A. M., van Duijn, E., Roos, R. A. C., Craufurd, D., Rickards, H., Landwehrmeyer, B., van der Mast, R. C., Giltay, E. J., Bachoud-Lévi, A. C., Bentivoglio, A. R., Biunno, I., Bonelli, R. M., Burgunder, J. M., Dunnett, S. B., Ferreira, J. J., Handley, O. J., Heiberg, A., Illmann, T., Landwehrmeyer, G. B., … Quarrell, O. (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, G. (1967). On chorea. Archives of Neurology, 17(3), 332–333. https://doi.org/10.1001/archneur.1967.00470270110014

Ivkovic, S., Polonskaia, O., Fariñas, I., & Ehrlich, M. E. (1997). Brain-derived neurotrophic factor regulates maturation of the DARPP-32 phenotype in striatal medium spiny neurons: Studies in

vivo and in vitro. Neuroscience, 79(2), 509–516. https://doi.org/10.1016/S0306-4522(96)00684-7

Jankovic, J., & Beach, J. (1997). Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology, 48(2), 358–362. https://doi.org/10.1212/WNL.48.2.358

Janssen, L. K., Sescousse, G., Hashemi, M. M., Timmer, M. H. M., Huurne, N. P. ter, Geurts, D. E. M., & Cools, R. (2015). Abnormal modulation of reward versus punishment learning by a dopamine D2-receptor antagonist in pathological gamblers. Psychopharmacology, 232(18), 3345. https://doi.org/10.1007/S00213-015-3986-Y

Janus, C., & Golde, T. (2014). The effect of brief neonatal cryoanesthesia on physical development and adult cognitive function in mice. Behavioural Brain Research, 259, 253–260. https://doi.org/10.1016/J.BBR.2013.11.010

Jensen, P., Fenger, K., Bolwig, T., & Sorensen, S. A. (1998). Crime in Huntington's disease: a study of registered offences among patients, relatives, and controls. Journal of Neurology, Neurosurgery, and Psychiatry, 65(4), 467. https://doi.org/10.1136/JNNP.65.4.467

Jentsch, J. D., Ashenhurst, J. R., Cervantes, M. C., James, A. S., Groman, S. M., & Pennington, Z. T. (2014). Dissecting Impulsivity and its Relationships to Drug Addictions. Annals of the New York Academy of Sciences, 1327(1), 1. https://doi.org/10.1111/NYAS.12388

Jeong, H., Cohen, D. E., Cui, L., Supinski, A., Savas, J. N., Mazzulli, J. R., Yates, J. R., Bordone, L., Guarente, L., & Krainc, D. (2011). Sirt1 mediates neuroprotection from mutant huntingtin by activation of the TORC1 and CREB transcriptional pathway. Nature Medicine 2011 18:1, 18(1), 159–165. https://doi.org/10.1038/nm.2559

Jhang, C. L., Huang, T. N., Hsueh, Y. P., & Liao, W. (2017). Mice lacking cyclin-dependent kinase-like 5 manifest autistic and ADHD-like behaviors. Human Molecular Genetics, 26(20), 3922–3934. https://doi.org/10.1093/HMG/DDX279

Jhanjee, A., Anand, K. S., & Bajaj, B. K. (2011). Hypersexual features in huntington's disease. Singapore Medical Journal, 52(6), 131–133.

Ji, W., Li, T., Pan, Y., Tao, H., Ju, K., Wen, Z., Fu, Y., An, Z., Zhao, Q., Wang, T., He, L., Feng, G., Yi, Q., & Shi, Y. (2013). CNTNAP2 is significantly associated with schizophrenia and major depression in the Han Chinese population. Psychiatry Research, 207(3), 225–228. https://doi.org/10.1016/j.psychres.2012.09.024

Jiang, M., Wang, J., Fu, J., Du, L., Jeong, H., West, T., Xiang, L., Peng, Q., Hou, Z., Cai, H., Seredenina, T., Arbez, N., Zhu, S., Sommers, K., Qian, J., Zhang, J., Mori, S., Yang, X. W., Tamashiro, K. L. K., … Duan, W. (2011). Neuroprotective role of Sirt1 in mammalian models of Huntington's disease through activation of multiple Sirt1 targets. Nature Medicine 2011 18:1, 18(1), 153–158. https://doi.org/10.1038/nm.2558

Jiang, Y., Chadwick, S. R., & Lajoie, P. (2016). Endoplasmic reticulum stress: The cause and solution to Huntington's disease? Brain Research, 1648, 650–657. https://doi.org/10.1016/J.BRAINRES.2016.03.034

Jimenez-Sanchez, M., Licitra, F., Underwood, B. R., & Rubinsztein, D. C. (2017). Huntington's Disease: Mechanisms of Pathogenesis and Therapeutic Strategies. Cold Spring Harbor Perspectives in Medicine, 7(7), 1–22. https://doi.org/10.1101/CSHPERSPECT.A024240

Johnson, M. A., Rajan, V., Miller, C. E., & Wightman, R. M. (2006). Dopamine release is severely compromised in the R6/2 mouse model of Huntington's disease. Journal of Neurochemistry, 97(3), 737–746. https://doi.org/10.1111/J.1471-4159.2006.03762.X

REFERENCES

Jones, K. R., Fariñas, I., Backus, C., & Reichardt, L. F. (1994). Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development. Cell, 76(6), 989–999. https://doi.org/10.1016/0092-8674(94)90377-8

Joshi, P. R., Wu, N. P., André, V. M., Cummings, D. M., Cepeda, C., Joyce, J. A., Carroll, J. B., Leavitt, B. R., Hayden, M. R., Levine, M. S., & Bamford, N. S. (2009). Age-dependent alterations of corticostriatal activity in the YAC128 mouse model of huntington disease. Journal of Neuroscience, 29(8), 2414–2427. https://doi.org/10.1523/JNEUROSCI.5687-08.2009

Joyce, J. N., Lexow, N., Bird, E., & Winokur, A. (1988). Organization of dopamine D1 and D2 receptors in human striatum: Receptor autoradiographic studies in Huntington's disease and schizophrenia. Synapse, 2(5), 546–557. https://doi.org/10.1002/SYN.890020511

Jupp, B., Caprioli, D., Saigal, N., Reverte, I., Shrestha, S., Cumming, P., Everitt, B. J., Robbins, T. W., & Dalley, J. W. (2013). Dopaminergic and GABA-ergic markers of impulsivity in rats: evidence for anatomical localisation in ventral striatum and prefrontal cortex. European Journal of Neuroscience, 37(9), 1519–1528. https://doi.org/10.1111/EJN.12146

Kaestner, K. H., Knöchel, W., & Martínez, D. E. (2000). Unified nomenclature for the winged helix/forkhead transcription factors. Genes & Development, 14(2), 142–146. https://doi.org/10.1101/GAD.14.2.142

Kantor, S., Szabo, L., Varga, J., Cuesta, M., & Morton, A. J. (2013). Progressive sleep and electroencephalogram changes in mice carrying the Huntington's disease mutation. Brain, 136(7), 2147–2158. https://doi.org/10.1093/BRAIN/AWT128

Kast, R. J., Lanjewar, A. L., Smith, C. D., & Levitt, P. (2019). FOXP2 exhibits projection neuron class specific expression, but is not required for multiple aspects of cortical histogenesis. ELife, 8. https://doi.org/10.7554/ELIFE.42012

Katoh, M., & Katoh, M. (2004). Human FOX gene family (Review). International Journal of Oncology, 25(5), 1495–1500. https://doi.org/10.3892/IJO.25.5.1495

KE, A. (2011). Huntington's disease. Handbook of Clinical Neurology, 100, 15–24. https://doi.org/10.1016/B978-0-444-52014-2.00002-1

Kegel, K. B., Meloni, A. R., Yi, Y., Kim, Y. J., Doyle, E., Cuiffo, B. G., Sapp, E., Wang, Y., Qin, Z. H., Don Chen, J., Nevins, J. R., Aronin, N., & Difiglia, M. (2002). Huntingtin is present in the nucleus, interacts with the transcriptional corepressor C-terminal binding protein, and represses transcription. Journal of Biological Chemistry, 277(9), 7466–7476. https://doi.org/10.1074/jbc.M103946200

Kerr, K. L., Avery, J. A., Barcalow, J. C., Moseman, S. E., Bodurka, J., Bellgowan, P. S. F., & Simmons, W. K. (2015). Trait impulsivity is related to ventral ACC and amygdala activity during primary reward anticipation. Social Cognitive and Affective Neuroscience, 10(1), 36–42. https://doi.org/10.1093/scan/nsu023

Khanzada, N. S., Butler, M. G., & Manzard, A. M. (2017). Geneanalytics pathway analysis and genetic overlap among autism spectrum disorder, bipolar disorder and Schizophrenia. International Journal of Molecular Sciences, 18(3). https://doi.org/10.3390/ijms18030527

Kieburtz, K., Feigin, A., McDermott, M., Como, P., Abwender, D., Zimmerman, C., Hickey, C., Orme, C., Claude, K., Sotack, J., Greenamyre, J. T., Dunn, C., & Shoulson, I. (1996). A controlled trial of remacemide hydrochloride in Huntington's disease. Movement Disorders, 11(3), 273–277. https://doi.org/10.1002/mds.870110310

Kim, B. S., & Im, H. I. (2019). The role of the dorsal striatum in choice impulsivity. Annals of the New York Academy of Sciences, 1451(1), 92–111. https://doi.org/10.1111/NYAS.13961

King, J. A., Tenney, J., Rossi, V., Colamussi, L., & Burdick, S. (2003). Neural Substrates Underlying Impulsivity. Annals of the New York Academy of Sciences, 1008, 160–169. https://doi.org/10.1196/ANNALS.1301.017

Kirkwood, S. C., Su, J. L., Conneally, P. M., & Foroud, T. (2001). Progression of symptoms in the early and middle stages of Huntington disease. Archives of Neurology, 58(2), 273–278. https://doi.org/10.1001/archneur.58.2.273

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1987). Elevated serotonin and reduced dopamine in subregionally divided Huntington's disease striatum. Annals of Neurology, 22(3), 386–389. https://doi.org/10.1002/ANA.410220318

Klapstein, G. J., Fisher, R. S., Zanjani, H., Cepeda, C., Jokel, E. S., Chesselet, M. F., & Levine, M. S. (2001). Electrophysiological and morphological changes in striatal spiny neurons in R6/2 Huntington's disease transgenic mice. Journal of Neurophysiology, 86(6), 2667–2677. http://www.ncbi.nlm.nih.gov/pubmed/11731527

Kolodziejczyk, K., & Raymond, L. A. (2016). Differential changes in thalamic and cortical excitatory synapses onto striatal spiny projection neurons in a Huntington disease mouse model. Neurobiology of Disease, 86, 62–74. https://doi.org/10.1016/J.NBD.2015.11.020

Koroshetz, BG, J., BR, R., & MF, B. (1997). Energy metabolism defects in Huntington's disease and effects of coenzyme Q10. Annals of Neurology, 41(2), 160–165. https://doi.org/10.1002/ANA.410410206

Koshikawa, N., Mori, E., Oka, K., Nomura, H., Yatsushige, N., & Maruyama, Y. (1989). Effects of SCH23390 injection into the dorsal striatum and nucleus accumbens on methamphetamine-induced gnawing and hyperlocomotion in rats. The Journal of Nihon University School of Dentistry, 31(2), 451–457. https://doi.org/10.2334/josnusd1959.31.451

Kosubek-Langer, J., & Scharff, C. (2020). Dynamic FoxP2 levels in male zebra finches are linked to morphology of adult-born Area X medium spiny neurons. Scientific Reports 2020 10:1, 10(1), 1–11. https://doi.org/10.1038/s41598-020-61740-6

Kreitzer, A. C., & Malenka, R. C. (2008). Striatal plasticity and basal ganglia circuit function. Neuron, 60(4), 543–554. https://doi.org/10.1016/j.neuron.2008.11.005

Kremer, B., Goldberg, P., Andrew, S. E., Theilmann, J., Telenius, H., Zeisler, J., Squitieri, F., Lin, B., Bassett, A., Almqvist, E., Bird, T. D., & Hayden, M. R. (1994). A Worldwide Study of the Huntington's Disease Mutation: The Sensitivity and Specificity of Measuring CAG Repeats. New England Journal of Medicine, 330(20), 1401–1406. https://doi.org/10.1056/nejm199405193302001

Kwok, R. P. S., Lundblad, J. R., Chrivia, J. C., Richards, J. P., Bächinger, H. P., Brennan, R. G., Roberts, S. G. E., Green, M. R., & Goodman, R. H. (1994). Nuclear protein CBP is a coactivator for the transcription factor CREB. Nature, 370(6486), 223–226. https://doi.org/10.1038/370223A0

Lai, C. S. L., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F., & Monaco, A. P. (2001). A forkhead-domain gene is mutated in a severe speech and language disorder. Nature 2001 413:6855, 413(6855), 519–523. https://doi.org/10.1038/35097076

REFERENCES

Lai, C. S. L., Gerrelli, D., Monaco, A. P., Fisher, S. E., & Copp, A. J. (2003). FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. Brain, 126(11), 2455–2462. https://doi.org/10.1093/brain/awg247

Landwehrmeyer, G. B., McNeil, S. M., Dure, L. S., Ge, P., Aizawa, H., Huang, Q., Ambrose, C. M., Duyao, M. P., Bird, E. D., Bonilla, E., de Young, M., Avila-Gonzales, A. J., Wexler, N. S., DiFiglia, M., Gusella, J. F., MacDonald, M. E., Penney, J. B., Young, A. B., & Vonsattel, J. -P. (1995). Huntington's disease gene: Regional and cellular expression in brain of normal and affected individuals. Annals of Neurology, 37(2), 218–230. https://doi.org/10.1002/ana.410370213

Landwehrmeyer, G. B., Dubois, B., de Yébenes, J. G., Kremer, B., Gaus, W., Kraus, P. H., Przuntek, H., Dib, M., Doble, A., Fischer, W., & Ludolph, A. C. (2007). Riluzole in Huntington's disease: A 3-year, randomized controlled study. Annals of Neurology, 62(3), 262–272. https://doi.org/10.1002/ana.21181

Lane, J. M., Liang, J., Vlasac, I., Anderson, S. G., Bechtold, D. A., Bowden, J., Emsley, R., Gill, S., Little, M. A., Luik, A. I., Loudon, A., Scheer, F. A. J. L., Purcell, S. M., Kyle, S. D., Lawlor, D. A., Zhu, X., Redline, S., Ray, D. W., Rutter, M. K., & Saxena, R. (2017). Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. Nature Genetics, 49(2), 274–281. https://doi.org/10.1038/ng.3749

Langbehn, D. R., Paulsen, J. S., & Group, T. H. S. (2007). Predictors of diagnosis in Huntington disease. Neurology, 68(20), 1710–1717. https://doi.org/10.1212/01.WNL.0000261918.90053.96

Lapper, S. R., & Bolam, J. P. (1992). Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. Neuroscience, 51(3), 533–545. https://doi.org/10.1016/0306-4522(92)90293-B

Lee, S. T., Chu, K., Park, J. E., Kang, L., Ko, S. Y., Jung, K. H., & Kim, M. (2006). Memantine reduces striatal cell death with decreasing calpain level in 3-nitropropionic model of Huntington's disease. Brain Research, 1118(1), 199–207. https://doi.org/10.1016/j.brainres.2006.08.035

Lei, W., Deng, Y., Liu, B., Mu, S., Guley, N. M., Wong, T., & Reiner, A. (2013). Confocal laser scanning microscopy and ultrastructural study of VGLUT2 thalamic input to striatal projection neurons in rats. Journal of Comparative Neurology, 521(6), 1354–1377. https://doi.org/10.1002/CNE.23235

Lelos, M. J., & Dunnett, S. B. (2018). Generating Excitotoxic Lesion Models of Huntington's Disease. Methods in Molecular Biology, 1780, 209–220. https://doi.org/10.1007/978-1-4939-7825-0_11

Levine, M. S., Klapstein, G. J., Koppel, A., Gruen, E., Cepeda, C., Vargas, M. E., Jokel, E. S., Carpenter, E. M., Zanjani, H., Hurst, R. S., Efstratiadis, A., Zeitlin, S., & Chesselet, M. F. (1999). Enhanced sensitivity to N-methyl-D-aspartate receptor activation in transgenic and knockin mouse models of Huntington's disease. Journal of Neuroscience Research, 58(4), 515–532. https://doi.org/10.1002/(SICI)1097-4547(19991115)58:4<515::AID-JNR5>3.0.CO;2-F

Levine, M. S., Cepeda, C., & André, V. M. (2010). Location, Location, Location: Contrasting Roles of Synaptic and Extrasynaptic NMDA Receptors in Huntington's Disease. Neuron, 65(2), 145–147. https://doi.org/10.1016/J.NEURON.2010.01.010

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. Journal of Neuropsychiatry and Clinical Neurosciences, 10(3), 314–319. https://doi.org/10.1176/jnp.10.3.314

Li, J., Dai, S., Chen, X., Liang, X., Qu, L., Jiang, L., Guo, M., Zhou, Z., Wei, H., Zhang, H., Chen, Z., Chen, L., & Chen, Y. (2021). Mechanism of forkhead transcription factors binding to a novel palindromic DNA site. Nucleic Acids Research, 49(6), 3573–3583. https://doi.org/10.1093/NAR/GKAB086

Li, S. H., Schilling, G., Young, W. S., Li, X., Margolis, R. L., Stine, O. C., Wagster, M. v., Abbott, M. H., Franz, M. L., Ranen, N. G., Folstein, S. E., Hedreen, J. C., & Ross, C. A. (1993). Huntington's disease gene (IT15) is widely expressed in human and rat tissues. Neuron, 11(5), 985–993. https://doi.org/10.1016/0896-6273(93)90127-D

Li, S., Weidenfeld, J., & Morrisey, E. E. (2004). Transcriptional and DNA Binding Activity of the Foxp1/2/4 Family Is Modulated by Heterotypic and Homotypic Protein Interactions. Molecular and Cellular Biology, 24(2), 809–822. https://doi.org/10.1128/mcb.24.2.809-822.2004

Li, T., Zeng, Z., Zhao, Q., Wang, T., Huang, K., Li, J., Li, Y., Liu, J., Wei, Z., Wang, Y., Feng, G., He, L., & Shi, Y. (2013). FoxP2 is significantly associated with schizophrenia and major depression in the Chinese Han Population. World Journal of Biological Psychiatry, 14(2), 146–150. https://doi.org/10.3109/15622975.2011.615860

Li, W., Serpell, L. C., Carter, W. J., Rubinsztein, D. C., & Huntington, J. A. (2006). Expression and characterization of full-length human huntingtin, an elongated HEAT repeat protein. Journal of Biological Chemistry, 281(23), 15916–15922. https://doi.org/10.1074/jbc.M511007200

Li, X., Branch, C. A., & DeLisi, L. E. (2009). Language pathway abnormalities in schizophrenia: A review of fMRI and other imaging studies. Current Opinion in Psychiatry, 22(2), 131–139. https://doi.org/10.1097/YCO.0B013E328324BC43

Liégeois, F., Baldeweg, T., Connelly, A., Gadian, D. G., Mishkin, M., & Vargha-Khadem, F. (2003). Language fMRI abnormalities associated with FOXP2 gene mutation. Nature Neuroscience 2003 6:11, 6(11), 1230–1237. https://doi.org/10.1038/NN1138

Lin, C. H., Tallaksen-Greene, S., Chien, W. M., Cearley, J. A., Jackson, W. S., Crouse, A. B., Ren, S., Li, X. J., Albin, R. L., & Detloff, P. J. (2001). Neurological abnormalities in a knock-in mouse model of Huntington's disease. Human Molecular Genetics, 10(2), 137–144. https://doi.org/10.1093/hmg/10.2.137

Lin, D., Boyle, M. P., Dollar, P., Lee, H., Lein, E. S., Perona, P., & Anderson, D. J. (2011). Functional identification of an aggression locus in the mouse hypothalamus. Nature 2011 470:7333, 470(7333), 221–226. https://doi.org/10.1038/nature09736

Linden, J., James, A. S., Mcdaniel, C., & David Jentsch, J. (2018). Disorders of the Nervous System Dopamine D2 Receptors in Dopaminergic Neurons Modulate Performance in a Reversal Learning Task in Mice. https://doi.org/10.1523/ENEURO.0229-17.2018

Lione, L. A., Carter, R. J., Hunt, M. J., Bates, G. P., Morton, A. J., & Dunnett, S. B. (1999). Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. Journal of Neuroscience, 19(23), 10428–10437. https://doi.org/10.1523/jneurosci.19-23-10428.1999

Lischinsky, J. E., & Lin, D. (2020). Neural mechanisms of aggression across species. Nature Neuroscience 2020 23:11, 23(11), 1317–1328. https://doi.org/10.1038/S41593-020-00715-2

REFERENCES

Hachigian, L. J., Carmona, V., Fenster, R. J., Kulicke, R., Heilbut, A., Sittler, A., Pereira de Almeida, L., Mesirov, J. P., Gao, F., Kolaczyk, E. D., & Heiman, M. (2017). Control of Huntington's Disease-Associated Phenotypes by the Striatum-Enriched Transcription Factor Foxp2. Cell Reports, 21(10), 2688–2695. https://doi.org/10.1016/j.celrep.2017.11.018

Loh, D. H., Kudo, T., Truong, D., Wu, Y., & Colwell, C. S. (2013). The Q175 Mouse Model of Huntington's Disease Shows Gene Dosage- and Age-Related Decline in Circadian Rhythms of Activity and Sleep. PLOS ONE, 8(7), e69993. https://doi.org/10.1371/JOURNAL.PONE.0069993

Louis, A. S. C. S. T., Yusuff, T., Cassar, M., Thomas, E., Kretzschmar, D., & D'Mello, S. R. (2017). Reduced expression of FoxpI as a contributing factor in huntington's disease. Journal of Neuroscience, 37(27), 6575–6587. https://doi.org/10.1523/JNEUROSCI.3612-16.2017

Lu, M. M., Li, S., Yang, H., & Morrisey, E. E. (2002). Foxp4: a novel member of the Foxp subfamily of winged-helix genes co-expressed with Foxp1 and Foxp2 in pulmonary and gut tissues. Mechanisms of Development, 119(SUPPL. 1), S197–S202. https://doi.org/10.1016/S0925-4773(03)00116-3

Lucetti, C., Gambaccini, G., Bernardini, S., Dell'Agnello, G., Petrozzi, L., Rossi, G., & Bonuccelli, U. (2002). Amantadine in Huntington's disease: Open-label video-blinded study. Neurological Sciences, 23(SUPPL. 2). https://doi.org/10.1007/s100720200081

Lüesse, H. G., Schiefer, J., Spruenken, A., Puls, C., Block, F., & Kosinski, C. M. (2001). Evaluation of R6/2 HD transgenic mice for therapeutic studies in Huntington's disease: behavioral testing and impact of diabetes mellitus. Behavioural Brain Research, 126(1–2), 185–195. https://doi.org/10.1016/S0166-4328(01)00261-3

Luthi-Carter, R., Strand, A., Peters, N. L., Solano, S. M., Hollingsworth, Z. R., Menon, A. S., Frey, A. S., Spektor, B. S., Penney, E. B., Schilling, G., Ross, C. A., Borchelt, D. R., Tapscott, S. J., Young, A. B., Cha, J.-H. J., & Olson, J. M. (2000). Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Human Molecular Genetics, 9(9), 1259–1271. https://doi.org/10.1093/HMG/9.9.1259

Luthi-Carter, R., Hanson, S. A., Strand, A. D., Bergstrom, D. A., Chun, W., Peters, N. L., Woods, A. M., Chan, E. Y., Kooperberg, C., Krainc, D., Young, A. B., Tapscott, S. J., & Olson, J. M. (2002). Dysregulation of gene expression in the R6/2 model of polyglutamine disease: parallel changes in muscle and brain. Human Molecular Genetics, 11(17), 1911–1926. https://doi.org/10.1093/HMG/11.17.1911

Lutz, B., Häring, M., Enk, V., Aparisi Rey, A., Loch, S., Ruiz De Azua, I., Monory, K., Weber, T., & Bartsch, D. (2015). Cannabinoid type-1 receptor signaling in central serotonergic neurons regulates anxiety-like behavior and sociability. Frontiers in Behavioral Neuroscience, 0(september), 235. https://doi.org/10.3389/FNBEH.2015.00235

MacDermot, K. D., Bonora, E., Sykes, N., Coupe, A. M., Lai, C. S. L., Vernes, S. C., Vargha-Khadem, F., McKenzie, F., Smith, R. L., Monaco, A. P., & Fisher, S. E. (2005). Identification of FOXP2 truncation as a novel cause of developmental speech and language deficits. American Journal of Human Genetics, 76(6), 1074–1080. https://doi.org/10.1086/430841

Mangiarini, L., Sathasivam, K., Seller, M., Cozens, B., Harper, A., Hetherington, C., Lawton, M., Trottier, Y., Lehrach, H., Davies, S. W., & Bates, G. P. (1996). Exon 1 of the HD Gene with an Expanded CAG Repeat Is Sufficient to Cause a Progressive Neurological Phenotype in Transgenic Mice. Cell, 87(3), 493–506. https://doi.org/10.1016/S0092-8674(00)81369-0

Manita, S., Suzuki, T., & Larkum, M. E. (2015). A Top-Down Cortical Circuit for Accurate Sensory Perception. Neuron, 86, 1304–1316. https://doi.org/10.1016/j.neuron.2015.05.006

Marano, M., Migliore, S., Maffi, S., Consoli, F., Aless, Luca, ro de, Mazzante, I., Ferdin, & Squitieri, o. (2017). Children with Mild CAG Repeat Expansion in HTT Gene Showing Psychiatric but not Neurological Presentation: Is It One More Shade of Huntington Disease? Journal of Alzheimers Disease & Parkinsonism 2017 7:3, 7(3), 1–5. https://doi.org/10.4172/2161-0460.1000335

Marco, S., Giralt, A., Petrovic, M. M., Pouladi, M. A., Martínez-Turrillas, R., Martínez-Hernández, J., Kaltenbach, L. S., Torres-Peraza, J., Graham, R. K., Watanabe, M., Luján, R., Nakanishi, N., Lipton, S. A., Lo, D. C., Hayden, M. R., Alberch, J., Wesseling, J. F., & Pérez-Otaño, I. (2013). Suppressing aberrant GluN3A expression rescues synaptic and behavioral impairments in Huntington's disease models. Nature Medicine, 19(8), 1030–1038. https://doi.org/10.1038/nm.3246

Marder, K., Zhao, H., Myers, R. H., Cudkowicz, M., Kayson, E., Kieburtz, K., Orme, C., Paulsen, J., Penney, J. B., Siemers, E., & Shoulson, I. (2000). Rate of functional decline in Huntington's disease. Neurology, 54(2), 452–458. https://doi.org/10.1212/wnl.54.2.452

Maricic, T., Günther, V., Georgiev, O., Gehre, S., Ćurlin, M., Schreiweis, C., Naumann, R., Burbano, H. A., Meyer, M., Lalueza-Fox, C., de la Rasilla, M., Rosas, A., Gajović, S., Kelso, J., Enard, W., Schaffner, W., & Pääbo, S. (2013). A Recent Evolutionary Change Affects a Regulatory Element in the Human FOXP2 Gene. Molecular Biology and Evolution, 30(4), 844–852. https://doi.org/10.1093/MOLBEV/MSS271

Marshall, F. J. (2006). Tetrabenazine as antichorea therapy in Huntington disease: A randomized controlled trial. Neurology, 66(3), 366–372. https://doi.org/10.1212/01.wnl.0000198586.85250.13

Mason, S. T, & Fibiger, H. C. (1978). Kainic acid lesions of the striatum: behavioural sequalae similar to Huntington's chorea. Brain Research, 155(2), 313–329. https://doi.org/10.1016/0006-8993(78)91025-9

Massioui, N. el, Lamirault, C., Yagüe, S., Adjeroud, N., Garces, D., Maillard, A., Tallot, L., Yu-Taeger, L., Riess, O., Allain, P., Nguyen, H. P., Hörsten, S. von, & Doyère, V. (2016). Impaired Decision Making and Loss of Inhibitory-Control in a Rat Model of Huntington Disease. Frontiers in Behavioral Neuroscience, 10(OCT). https://doi.org/10.3389/FNBEH.2016.00204

Massouh, M., Wallman, M. J., Pourcher, E., & Parent, A. (2008). The fate of the large striatal interneurons expressing calretinin in Huntington's disease. Neuroscience Research, 62(4), 216–224. https://doi.org/10.1016/J.NEURES.2008.08.007

Matsuoka, Y., Furuyashiki, T., Yamada, K., Nagai, T., Bito, H., Tanaka, Y., Kitaoka, S., Ushikubi, F., Nabeshima, T., & Narumiya, S. (2005). Prostaglandin E receptor EP1 controls impulsive behavior under stress. www.pnas.orgcgidoi10.1073pnas.0504908102

Matsuura, K., Kabuto, H., Makino, H., & Ogawa, N. (1997). Pole test is a useful method for evaluating the mouse movement disorder caused by striatal dopamine depletion. Journal of Neuroscience Methods, 73(1), 45–48. https://doi.org/10.1016/S0165-0270(96)02211-X

Mazarakis, N. K., Cybulska-Klosowicz, A., Grote, H., Pang, T., Dellen, A. van, Kossut, M., Blakemore, C., & Hannan, A. J. (2005). Behavioral/Systems/Cognitive Deficits in Experience-Dependent Cortical Plasticity and Sensory-Discrimination Learning in Presymptomatic Huntington's Disease Mice. https://doi.org/10.1523/JNEUROSCI.4320-04.2005

McBride, J. L., Ramaswamy, S., Gasmi, M., Bartus, R. T., Herzog, C. D., Brandon, E. P., Zhou, L., Pitzer, M. R., Berry-Kravis, E. M., & Kordower, J. H. (2006). Viral delivery of glial cell line-derived neurotrophic factor improves behavior and protects striatal neurons in a mouse model of Huntington's disease. Proceedings of the National Academy of Sciences of the United States of America, 103(24), 9345. https://doi.org/10.1073/PNAS.0508875103

McCusker, E., & Loy, C. T. (2014). The Many Facets of Unawareness in Huntington Disease. Tremor and Other Hyperkinetic Movements, 4(1). https://doi.org/10.7916/D8FJ2FD3

McDonell, K. E., Ciriegio, A. E., Pfalzer, A. C., Hale, L., Shiino, S., Riordan, H., Moroz, S., Darby, R. R., Compas, B. E., & Claassen, D. O. (2020). Risk-Taking Behaviors in Huntington's Disease. Journal of Huntington's Disease, 9(4), 359–369. https://doi.org/10.3233/JHD-200431

McEvilly, R. J., Diaz, M. O. de, Schonemann, M. D., Hooshmand, F., & Rosenfeld, M. G. (2002). Transcriptional Regulation of Cortical Neuron Migration by POU Domain Factors. Science, 295(5559), 1528–1532. https://doi.org/10.1126/SCIENCE.1067132

Mcgarry, A., Mcdermott, M. P., Kieburtz, K., Fung, W. L. A., Mccusker, E., Peng, J., de Blieck, E. A., & Cudkowicz, M. (2019). Risk factors for suicidality in Huntington disease: An analysis of the 2CARE clinical trial. Neurology, 92(14), E1643–E1651. https://doi.org/10.1212/WNL.0000000000007244

McGeer, P. L., & McGeer, E. G. (1976). Enzymes associated with the metabolism of catecholamines, acetylcholine and gaba in human controls and patients with Parkinson's disease and Huntington's chorea. Journal of Neurochemistry, 26(1), 65–76. https://doi.org/10.1111/J.1471-4159.1976.TB04437.X

Medvedeva, V. P., Rieger, M. A., Vieth, B., Mombereau, C., Ziegenhain, C., Ghosh, T., Cressant, A., Enard, W., Granon, S., Dougherty, J. D., & Groszer, M. (2019). Altered social behavior in mice carrying a cortical Foxp2 deletion. Human Molecular Genetics, 28(5), 701–717. https://doi.org/10.1093/HMG/DDY372

Melief, E. J., McKinley, J. W., Lam, J. Y., Whiteley, N. M., Gibson, A. W., Neumaier, J. F., Henschen, C. W., Palmiter, R. D., Bamford, N. S., & Darvas, M. (2018). Loss of glutamate signaling from the thalamus to dorsal striatum impairs motor function and slows the execution of learned behaviors. Npj Parkinson's Disease 2018 4:1, 4(1), 1–11. https://doi.org/10.1038/s41531-018-0060-6

Melo, C. v., Okumoto, S., Gomes, J. R., Baptista, M. S., Bahr, B. A., Frommer, W. B., & Duarte, C. B. (2013). Spatiotemporal resolution of BDNF neuroprotection against glutamate excitotoxicity in cultured hippocampal neurons. Neuroscience, 237, 66–86. https://doi.org/10.1016/J.NEUROSCIENCE.2013.01.054

Menalled, L. B., Sison, J. D., Dragatsis, I., Zeitlin, S., & Chesselet, M. F. (2003). Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. Journal of Comparative Neurology, 465(1), 11–26. https://doi.org/10.1002/cne.10776

Menalled, L., El-Khodor, B. F., Patry, M., Suárez-Fariñas, M., Orenstein, S. J., Zahasky, B., Leahy, C., Wheeler, V., Yang, X. W., MacDonald, M., Morton, A. J., Bates, G., Leeds, J., Park, L., Howland, D., Signer, E., Tobin, A., & Brunner, D. (2009). Systematic behavioral evaluation of Huntington's disease transgenic and knock-in mouse models. Neurobiology of Disease, 35(3), 319–336. https://doi.org/10.1016/J.NBD.2009.05.007

Menalled, L. B., Kudwa, A. E., Miller, S., Fitzpatrick, J., Watson-Johnson, J., Keating, N., Ruiz, M., Mushlin, R., Alosio, W., McConnell, K., Connor, D., Murphy, C., Oakeshott, S., Kwan, M.,

Beltran, J., Ghavami, A., Brunner, D., Park, L. C., Ramboz, S., & Howland, D. (2012). Comprehensive Behavioral and Molecular Characterization of a New Knock-In Mouse Model of Huntington's Disease: zQ175. PLOS ONE, 7(12), e49838. https://doi.org/10.1371/JOURNAL.PONE.0049838

Mendoza, E., & Scharff, C. (2017). Protein-Protein Interaction Among the FoxP Family Members and their Regulation of Two Target Genes, VLDLR and CNTNAP2 in the Zebra Finch Song System. Frontiers in Molecular Neuroscience, 0, 112. https://doi.org/10.3389/FNMOL.2017.00112

Metman, L. V., Morris, M. J., Farmer, C., Gillespie, M., Mosby, K., Wuu, J., & Chase, T. N. (2002). Huntington's disease: A randomized, controlled trial using the NMDA-antagonist amantadine. Neurology, 59(5), 694–699. https://doi.org/10.1212/wnl.59.5.694

Metz, G. A. S., Schwab, M. E., & Welzl, H. (2001). The effects of acute and chronic stress on motor and sensory performance in male Lewis rats. Physiology and Behavior, 72(1–2), 29–35. https://doi.org/10.1016/S0031-9384(00)00371-1

Miller, B. R., Walker, A. G., Barton, S. J., & Rebec, G. v. (2011). Dysregulated Neuronal Activity Patterns Implicate Corticostriatal Circuit Dysfunction in Multiple Rodent Models of Huntington's Disease. Frontiers in Systems Neuroscience, 0(MAY 2011), 26. https://doi.org/10.3389/FNSYS.2011.00026

Milnerwood, A. J., Gladding, C. M., Pouladi, M. A., Kaufman, A. M., Hines, R. M., Boyd, J. D., Ko, R. W. Y., Vasuta, O. C., Graham, R. K., Hayden, M. R., Murphy, T. H., & Raymond, L. A. (2010). Early Increase in Extrasynaptic NMDA Receptor Signaling and Expression Contributes to Phenotype Onset in Huntington's Disease Mice. Neuron, 65(2), 178–190. https://doi.org/10.1016/j.neuron.2010.01.008

Mirallave, A., Morales, M., Cabib, C., Muñoz, E. J., Santacruz, P., Gasull, X., & Valls-Sole, J. (2017). Sensory processing in Huntington's disease. Clinical Neurophysiology, 128(5), 689–696. https://doi.org/10.1016/J.CLINPH.2017.01.009

Mitra, S., Tsvetkov, A. S., & Finkbeiner, S. (2009). Single neuron ubiquitin-proteasome dynamics accompanying inclusion body formation in Huntington disease. Journal of Biological Chemistry, 284(7), 4398–4403. https://doi.org/10.1074/jbc.M806269200

Miyazaki, S., Tahara, Y., Colwell, C. S., Block, G. D., Nakamura, W., & Nakamura, T. J. (2021). Chronic methamphetamine uncovers a circadian rhythm in multiple-unit neural activity in the dorsal striatum which is independent of the suprachiasmatic nucleus. Neurobiology of Sleep and Circadian Rhythms, 11, 100070. https://doi.org/10.1016/J.NBSCR.2021.100070

Mizutani, A., Matsuzaki, A., Momoi, M. Y., Fujita, E., Tanabe, Y., & Momoi, T. (2007). Intracellular distribution of a speech/language disorder associated FOXP2 mutant. Biochemical and Biophysical Research Communications, 353(4), 869–874. https://doi.org/10.1016/J.BBRC.2006.12.130

Morgan, A., Fisher, S. E., Scheffer, I., & Hildebrand, M. (2017). FOXP2-Related Speech and Language Disorders. GeneReviews®. https://www.ncbi.nlm.nih.gov/books/NBK368474/

Morton, A. J., & Edwardson, J. M. (2001). Progressive depletion of complexin II in a transgenic mouse model of Huntington's disease. Journal of Neurochemistry, 76(1), 166–172. https://doi.org/10.1046/J.1471-4159.2001.00059.X

Morton, A. J., Faull, R. L. M., & Edwardson, J. M. (2001). Abnormalities in the synaptic vesicle fusion machinery in Huntington's disease. Brain Research Bulletin, 56(2), 111–117. https://doi.org/10.1016/S0361-9230(01)00611-6

Moses, T. E. H., Burmeister, M., & Greenwald, M. K. (2019). Heroin delay discounting and impulsivity: Modulation by DRD1 genetic variation. https://doi.org/10.1111/adb.12777

Mukamel, Z., Konopka, G., Wexler, E., Osborn, G. E., Dong, H., Bergman, M. Y., Levitt, P., & Geschwind, D. H. (2011). Regulation of MET by FOXP2, Genes Implicated in Higher Cognitive Dysfunction and Autism Risk. The Journal of Neuroscience, 31(32), 11437. https://doi.org/10.1523/JNEUROSCI.0181-11.2011

Murman, D. L., Giordani, B., Mellow, A. M., Johanns, J. R., Little, R. J. J. A., Hariharan, M., & Foster, N. L. (1997). Cognitive, behavioral, and motor effects of the NMDA antagonist ketamine in Huntington's disease. Neurology, 49(1), 153–161. https://doi.org/10.1212/WNL.49.1.153

Murmu, R. P., Li, W., Holtmaat, A., & Li, J.-Y. (2013). Dendritic Spine Instability Leads to Progressive Neocortical Spine Loss in a Mouse Model of Huntington's Disease. Journal of Neuroscience, 33(32), 12997–13009. https://doi.org/10.1523/JNEUROSCI.5284-12.2013

Murmu, R. P., Li, W., Szepesi, Z., & Li, J.-Y. (2015). Altered Sensory Experience Exacerbates Stable Dendritic Spine and Synapse Loss in a Mouse Model of Huntington's Disease. Journal of Neuroscience, 35(1), 287–298. https://doi.org/10.1523/JNEUROSCI.0244-14.2015

Murugan, M., Harward, S., Scharff, C., & Mooney, R. (2013). Diminished FoxP2 levels affect dopaminergic modulation of corticostriatal signaling important to song variability. Neuron, 80(6), 1464–1476. https://doi.org/10.1016/j.neuron.2013.09.021

Nakamoto, C., Kawamura, M., Nakatsukasa, E., Natsume, R., Takao, K., Watanabe, M., Abe, M., Takeuchi Id, T., & Sakimura, K. (2020). GluD1 knockout mice with a pure C57BL/6N background show impaired fear memory, social interaction, and enhanced depressive-like behavior. https://doi.org/10.1371/journal.pone.0229288

Nance, M. A., & Sanders, G. (1996). Characteristics of individuals with Huntington disease in long-term care. Movement Disorders, 11(5), 542–548. https://doi.org/10.1002/mds.870110509

Nance, M. A., Mathias-Hagen, V., Breningstall, G., Wick, M. J., & McGlennen, R. C. (1999). Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. Neurology, 52(2), 392–392. https://doi.org/10.1212/WNL.52.2.392

Nasir, J., Floresco, S. B., O'Kusky, J. R., Diewert, V. M., Richman, J. M., Zeisler, J., Borowski, A., Marth, J. D., Phillips, A. G., & Hayden, M. R. (1995). Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. Cell, 81(5), 811–823. https://doi.org/10.1016/0092-8674(95)90542-1

Naver, B., Stub, C., Møller, M., Fenger, K., Hansen, A. K., Hasholt, L., & Sørensen, S. A. (2003). Molecular and behavioral analysis of the R6/1 Huntington's disease transgenic mouse. Neuroscience, 122(4), 1049–1057. https://doi.org/10.1016/j.neuroscience.2003.08.053

Negishi, T., Takahashi, M., Matsunaga, Y., Hirano, S., & Tashiro, T. (2012). Diphenylarsinic acid increased the synthesis and release of neuroactive and vasoactive peptides in rat cerebellar astrocytes. Journal of Neuropathology and Experimental Neurology, 71(6), 468–479. https://doi.org/10.1097/NEN.0b013e3182561327

Neo, S. H., & Tang, B. L. (2018). Sirtuins as Modifiers of Huntington's Disease (HD) Pathology. Progress in Molecular Biology and Translational Science, 154, 105–145. https://doi.org/10.1016/BS.PMBTS.2017.11.013

NicNiocaill, B., Haraldsson, B., Hansson, O., O'Connor, W. T., & Brundin, P. (2001). Altered striatal amino acid neurotransmitter release monitored using microdialysis in R6/1 Huntington

transgenic mice. European Journal of Neuroscience, 13(1), 206–210. https://doi.org/10.1046/J.0953-816X.2000.01379.X

Niu, S., Yabut, O., & D'Arcangelo, G. (2008). The Reelin Signaling Pathway Promotes Dendritic Spine Development in Hippocampal Neurons. Journal of Neuroscience, 28(41), 10339–10348. https://doi.org/10.1523/JNEUROSCI.1917-08.2008

Norton, P., Barschke, P., Scharff, C., & Mendoza, E. (2019). Differential Song Deficits after Lentivirus-Mediated Knockdown of FoxP1, FoxP2, or FoxP4 in Area X of Juvenile Zebra Finches. Journal of Neuroscience, 39(49), 9782–9796. https://doi.org/10.1523/JNEUROSCI.1250-19.2019

Novak, M. J. U., & Tabrizi, S. J. (2010). Huntington's disease. BMJ, 340(7762), 34–40. https://doi.org/10.1136/BMJ.C3109

Novak, M. J. U., & Tabrizi, S. J. (2011). Huntington's disease: clinical presentation and treatment. International Review of Neurobiology, 98, 297–323. https://doi.org/10.1016/B978-0-12-381328-2.00013-4

Nucifora, F. C., Sasaki, M., Peters, M. F., Huang, H., Cooper, J. K., Yamada, M., Takahashi, H., Tsuji, S., Troncoso, J., Dawson, V. L., Dawson, T. M., & Ross, C. A. (2001). Interference by Huntingtin and Atrophin-1 with CBP-Mediated Transcription Leading to Cellular Toxicity. Science, 291(5512), 2423–2428. https://doi.org/10.1126/SCIENCE.1056784

Nucifora, J., Sasaki, M., Peters, M. F., Huang, H., Cooper, J. K., Yamada, M., Takahashi, H., Tsuji, S., Troncoso, J., Dawson, V. L., Dawson, T. M., & Ross, C. A. (2001). Interference by huntingtin and atrophin-1 with CBP-mediated transcription leading to cellular toxicity. Science, 291(5512), 2423–2428. https://doi.org/10.1126/science.1056784

Ogawa, N., Hirose, Y., Ohara, S., Ono, T., & Watanabe, Y. (1985). A simple quantitative bradykinesia test in MPTP-treated mice. Research Communications in Chemical Pathology and Pharmacology, 50(3), 435–441. https://europepmc-org.sire.ub.edu/article/med/3878557

Okamoto, S., Pouladi, M. A., Talantova, M., Yao, D., Xia, P., Ehrnhoefer, D. E., Zaidi, R., Clemente, A., Kaul, M., Graham, R. K., Zhang, D., Chen, H.-S. V., Tong, G., Hayden, M. R., & Lipton, S. A. (2009). Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. Nature Medicine, 15(12), 1407. https://doi.org/10.1038/NM.2056

Oostrom, V., PE, S., RA, R., & KL, L. (2007). 1H magnetic resonance spectroscopy in preclinical Huntington disease. Brain Research, 1168(1), 67–71. https://doi.org/10.1016/J.BRAINRES.2007.05.082

Oostrom, J. C. H. van, Dekker, M., Willemsen, A. T. M., Jong, B. M. de, Roos, R. A. C., & Leenders, K. L. (2009). Changes in striatal dopamine D2 receptor binding in pre-clinical Huntington's disease. European Journal of Neurology, 16(2), 226–231. https://doi.org/10.1111/J.1468-1331.2008.02390.X

Orth, M., Schippling, S., Schneider, S. A., Bhatia, K. P., Talelli, P., Tabrizi, S. J., & Rothwell, J. C. (2010). Abnormal motor cortex plasticity in premanifest and very early manifest Huntington disease. Journal of Neurology, Neurosurgery and Psychiatry, 81(3), 267–270. https://doi.org/10.1136/JNNP.2009.171926

Orvoen, S., Pla, P., Gardier, A. M., Saudou, F., & David, D. J. (2012). Huntington's disease knock-in male mice show specific anxiety-like behaviour and altered neuronal maturation. Neuroscience Letters, 507(2), 127–132. https://doi.org/10.1016/J.NEULET.2011.11.063

REFERENCES

O'Suilleabhain, P., & Dewey, R. B. (2003). A randomized trial of amantadine in Huntington disease. Archives of Neurology, 60(7), 996–998. https://doi.org/10.1001/archneur.60.7.996

Osumi, N. (2001). The role of Pax6 in brain patterning. In Tohoku Journal of Experimental Medicine (Vol. 193, Issue 3, pp. 163–174). Tohoku J Exp Med. https://doi.org/10.1620/tjem.193.163

Ozcelik, T., Akarsu, N., Uz, E., Caglayan, S., Gulsuner, S., Onat, O. E., Tan, M., & Tan, U. (2008). Mutations in the very low-density lipoprotein receptor VLDLR cause cerebellar hypoplasia and quadrupedal locomotion in humans. Proceedings of the National Academy of Sciences, 105(11), 4232–4236. https://doi.org/10.1073/PNAS.0710010105

Pairojana, T., Phasuk, S., Suresh, P., Huang, S. P., Pakaprot, N., Chompoopong, S., Hsieh, T. C., & Liu, I. Y. (2021). Age and gender differences for the behavioral phenotypes of 3xTg alzheimer's disease mice. Brain Research, 1762. https://doi.org/10.1016/J.BRAINRES.2021.147437

Pal, A., Severin, F., Lommer, B., Shevchenko, A., & Zerial, M. (2006). Huntingtin-HAP40 complex is a novel Rab5 effector that regulates early endosome motility and is up-regulated in Huntington's disease. Journal of Cell Biology, 172(4), 605–618. https://doi.org/10.1083/jcb.200509091

Paleacu, D., Giladi, N., Moore, O., Stern, A., Honigman, S., & Badarny, S. (2004). Tetrabenazine treatment in movement disorders. Clinical Neuropharmacology, 27(5), 230–233. https://doi.org/10.1097/01.wnf.0000136892.24629.96

Pan, W. X., Mao, T., & Dudman, J. T. (2010). Inputs to the Dorsal Striatum of the Mouse Reflect the Parallel Circuit Architecture of the Forebrain. Frontiers in Neuroanatomy, 0(DEC), 147. https://doi.org/10.3389/FNANA.2010.00147

Pang, T. Y. C., Du, X., Zajac, M. S., Howard, M. L., & Hannan, A. J. (2009). Altered serotonin receptor expression is associated with depression-related behavior in the R6/1 transgenic mouse model of Huntington's disease. Human Molecular Genetics, 18(4), 753–766. https://doi.org/10.1093/HMG/DDN385

Papadia, S., & Hardingham, G. E. (2016). The Dichotomy of NMDA Receptor Signaling: Http://Dx.Doi.Org/10.1177/1073858407013006040 1, 13(6), 572–579. https://doi.org/10.1177/1073858407013006040 1

Parievsky, A., Moore, C., Kamdjou, T., Cepeda, C., Meshul, C. K., & Levine, M. S. (2017). Differential electrophysiological and morphological alterations of thalamostriatal and corticostriatal projections in the R6/2 mouse model of Huntington's disease. Neurobiology of Disease, 108, 29–44. https://doi.org/10.1016/J.NBD.2017.07.020

Parker, P. R., Lalive, A. L., & Kreitzer, A. C. (2016). Pathway-Specific Remodeling of Thalamostriatal Synapses in Parkinsonian Mice. https://doi.org/10.1016/j.neuron.2015.12.038

Parsons, M. P., Kang, R., Buren, C., Dau, A., Southwell, A. L., Doty, C. N., Sanders, S. S., Hayden, M. R., & Raymond, L. A. (2014). Bidirectional Control of Postsynaptic Density-95 (PSD-95) Clustering by Huntingtin. The Journal of Biological Chemistry, 289(6), 3518. https://doi.org/10.1074/JBC.M113.513945

Patil, S. N., & Brid, S. v. (2010). Relative role of neural substrates in the aggressive behavior of rats. Journal of Basic and Clinical Physiology and Pharmacology, 21(4), 357–368.

Paulsen, J. S., Zimbelman, J. L., Hinton, S. C., Langbehn, D. R., Leveroni, C. L., Benjamin, M. L., Reynolds, N. C., & Rao, S. M. (2004). fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's disease. American Journal of Neuroradiology, 25(10), 1715–1721.

Peg Nopoulos, M. D., Vincent A. Magnotta, Ph. D., Ania Mikos, M. S., Henry Paulson, M. D. , Ph. D., Nancy C. Andreasen, M. D. , Ph. D., & Jane S. Paulsen, Ph. D. (2007). Morphology of the Cerebral Cortex in Preclinical Huntington's Disease. Https://Doi.Org/10.1176/Appi.Ajp.2007.06081266, 164(9), 1428–1434. https://doi.org/10.1176/APPI.AJP.2007.06081266

Peng, Q., Masuda, N., Jiang, M., Li, Q., Zhao, M., Ross, C. A., & Duan, W. (2008). The antidepressant sertraline improves the phenotype, promotes neurogenesis and increases BDNF levels in the R6/2 Huntington's disease mouse model. Experimental Neurology, 210(1), 154–163. https://doi.org/10.1016/J.EXPNEUROL.2007.10.015

Penzes, P., & Cahill, M. E. (2012). Deconstructing signal transduction pathways that regulate the actin cytoskeleton in dendritic spines. Cytoskeleton (Hoboken, N.J.), 69(7), 426. https://doi.org/10.1002/CM.21015

Perez, M. K., Paulson, H. L., Pendse, S. J., Saionz, S. J., Bonini, N. M., & Pittman, R. N. (1998). Recruitment and the role of nuclear localization in polyglutamine- mediated aggregation. Journal of Cell Biology, 143(6), 1457–1470. https://doi.org/10.1083/jcb.143.6.1457

Pérez-Navarro, E., Canudas, A. M., Åkerud, P., Alberch, J., & Arenas, E. (2000). Brain-Derived Neurotrophic Factor, Neurotrophin-3, and Neurotrophin-4/5 Prevent the Death of Striatal Projection Neurons in a Rodent Model of Huntington's Disease. Journal of Neurochemistry, 75(5), 2190–2199. https://doi.org/10.1046/J.1471-4159.2000.0752190.X

Petersén, Å., & Björkqvist, M. (2006). Hypothalamic-endocrine aspects in Huntington's disease. In European Journal of Neuroscience (Vol. 24, Issue 4, pp. 961–967). Eur J Neurosci. https://doi.org/10.1111/j.1460-9568.2006.04985.x

Petersen, C. C. H. (2007). The functional organization of the barrel cortex. In Neuron (Vol. 56, Issue 2, pp. 339–355). Cell Press. https://doi.org/10.1016/j.neuron.2007.09.017

Pflanz, S., Besson, J. A. O., Ebmeier, K. P., & Simpson, S. (1991). The clinical manifestation of mental disorder in Huntington's disease: a retrospective case record study of disease progression. Acta Psychiatrica Scandinavica, 83(1), 53–60. https://doi.org/10.1111/j.1600-0447.1991.tb05511.x

Picconi, B., Passino, E., Sgobio, C., Bonsi, P., Barone, I., Ghiglieri, V., Pisani, A., Bernardi, G., Ammassari-Teule, M., & Calabresi, P. (2006). Plastic and behavioral abnormalities in experimental Huntington's disease: A crucial role for cholinergic interneurons. Neurobiology of Disease, 22(1), 143–152. https://doi.org/10.1016/J.NBD.2005.10.009

Pine, A., Shiner, T., Seymour, B., & Dolan, R. J. (2010). Dopamine, Time, and Impulsivity in Humans. Journal of Neuroscience, 30(26), 8888–8896. https://doi.org/10.1523/JNEUROSCI.6028-09.2010

Pini, L., Jacquemot, C., Cagnin, A., Meneghello, F., Semenza, C., Mantini, D., & Vallesi, A. (2020). Aberrant brain network connectivity in presymptomatic and manifest Huntington's disease: A systematic review. Human Brain Mapping, 41(1), 256–269. https://doi.org/10.1002/HBM.24790

Plotkin, J. L., & Surmeier, D. J. (2015). Corticostriatal synaptic adaptations in Huntington's disease. Current Opinion in Neurobiology, 33, 53–62. https://doi.org/10.1016/J.CONB.2015.01.020

Pogoda, A., Chmielewska, N., Maciejak, P., & Szyndler, J. (2020). Transcriptional Dysregulation in Huntington's Disease: The Role in Pathogenesis and Potency for Pharmacological Targeting. Current Medicinal Chemistry, 28(14), 2783–2806. https://doi.org/10.2174/0929867327666200705225821

Pouladi, M. A., Graham, R. K., Karasinska, J. M., Xie, Y., Santos, R. D., Petersén, Å., & Hayden, M. R. (2009). Prevention of depressive behaviour in the YAC128 mouse model of Huntington disease by mutation at residue 586 of huntingtin. Brain, 132(4), 919–932. https://doi.org/10.1093/BRAIN/AWP006

Pouladi, M. A., Stanek, L. M., Xie, Y., Franciosi, S., Southwell, A. L., Deng, Y., Butland, S., Zhang, W., Cheng, S. H., Shihabuddin, L. S., & Hayden, M. R. (2012). Marked differences in neurochemistry and aggregates despite similar behavioural and neuropathological features of Huntington disease in the full-length BACHD and YAC128 mice. Human Molecular Genetics, 21(10), 2219–2232. https://doi.org/10.1093/hmg/dds037

Pradhan, J., Noakes, P. G., & Bellingham, M. C. (2019). The Role of Altered BDNF/TrkB Signaling in Amyotrophic Lateral Sclerosis. Frontiers in Cellular Neuroscience, 0, 368. https://doi.org/10.3389/FNCEL.2019.00368

Pringsheim, T., Wiltshire, K., Day, L., Dykeman, J., Steeves, T., & Jette, N. (2012). The incidence and prevalence of Huntington's disease: A systematic review and meta-analysis. Movement Disorders, 27(9), 1083–1091. https://doi.org/10.1002/MDS.25075

Puigdellívol, M., Cherubini, M., Brito, V., Giralt, A., Suelves, N., Ballesteros, J., Zamora-Moratalla, A., Martín, E. D., Eipper, B. A., Alberch, J., & Ginés, S. (2015). A role for Kalirin-7 in corticostriatal synaptic dysfunction in Huntington's disease. Human Molecular Genetics, 24(25), 7265–7285. https://doi.org/10.1093/HMG/DDV426

Quarrell, O. W. J., Nance, M. A., Nopoulos, P., Paulsen, J. S., Smith, J. A., & Squitieri, F. (2013). Managing juvenile Huntington's disease. Neurodegenerative Disease Management, 3(3), 267–276. https://doi.org/10.2217/NMT.13.18

Quinn, P. D., Stappenbeck, C. A., & Fromme, K. (2011). Collegiate heavy drinking prospectively predicts change in sensation seeking and impulsivity. Journal of Abnormal Psychology, 120(3), 543–556. https://doi.org/10.1037/a0023159

Quirion, J. G., & Parsons, M. P. (2019). The Onset and Progression of Hippocampal Synaptic Plasticity Deficits in the Q175FDN Mouse Model of Huntington Disease. Frontiers in Cellular Neuroscience, 0, 326. https://doi.org/10.3389/FNCEL.2019.00326

Raamsdonk, J. M. van, Pearson, J., Slow, E. J., Hossain, S. M., Leavitt, B. R., & Hayden, M. R. (2005). Cognitive Dysfunction Precedes Neuropathology and Motor Abnormalities in the YAC128 Mouse Model of Huntington's Disease. The Journal of Neuroscience, 25(16), 4169. https://doi.org/10.1523/JNEUROSCI.0590-05.2005

Ralph, M. R., Foster, R. G., Davis, F. C., & Menaker, M. (1990). Transplanted suprachiasmatic nucleus determines circadian period. Science, 247(4945), 975–978. https://doi.org/10.1126/science.2305266

Ramaswamy, S., McBride, J. L., & Kordower, J. H. (2007). Animal Models of Huntington's Disease. ILAR Journal, 48(4), 356–373. https://doi.org/10.1093/ILAR.48.4.356

Ranen, N. G., Stine, O. C., Abbott, M. H., Sherr, M., Codori, A.-M., Franz, M. L., Chao, N. I., Chung, A. S., Pleasant, N., Callahan, C., Kasch, L. M., Ghaffari, M., Chase, G. A., Kazazian, H. H., Brandt, J., Folstein, S. E., & Ross, C. A. (1995). Anticipation and Instability of IT-15 (CAG)N Repeats in Parent-Offspring Pairs with Huntington Disease. American Journal of Human Genetics, 57(3), 593. /pmc/articles/PMC1801258/?report=abstract

Rangel-Barajas, C., & Rebec, G. v. (2016). Dysregulation of Corticostriatal Connectivity in Huntington's Disease: A Role for Dopamine Modulation. Journal of Huntington's Disease, 5(4), 303–331. https://doi.org/10.3233/JHD-160221

Rao, W., Du, X., Zhang, Y., Yu, Q., Hui, L., Yu, Y., Kou, C., Yin, G., Zhu, X., Man, L., Soares, J. C., & Zhang, X. Y. (2017). Association between forkhead-box P2 gene polymorphism and clinical symptoms in chronic schizophrenia in a Chinese population. Journal of Neural Transmission 2017 124:7, 124(7), 891–897. https://doi.org/10.1007/S00702-017-1723-X

Raymond, L. A. (2017). Striatal synaptic dysfunction and altered calcium regulation in Huntington disease. Biochemical and Biophysical Research Communications, 483(4), 1051–1062. https://doi.org/10.1016/J.BBRC.2016.07.058

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

Rebok, G. W., Bylsma, F. W., Keyl, P. M., Brandt, J., & Folstein, S. E. (1995). Automobile driving in Huntington's disease. Movement Disorders, 10(6), 778–787. https://doi.org/10.1002/mds.870100611

Reiner, A., Albin, R. L., Anderson, K. D., D'amato, C. J., Penneyt, J. B., & Youngt, A. B. (1988). Differential loss of striatal projection neurons in Huntington disease (enkephalin/substance P/globus pallidus/substantia nigra/chorea). Proc. Natl. Acad. Sci. USA, 85, 5733–5737.

Reiner, A., Dragatsis, I., & Dietrich, P. (2011). Genetics and neuropathology of huntington's disease. International Review of Neurobiology, 98, 325. https://doi.org/10.1016/B978-0-12-381328-2.00014-6

Reiner, A., Shelby, E., Wang, H., Demarch, Z., Deng, Y., Guley, N. H., Hogg, V., Roxburgh, R., Tippett, L. J., Waldvogel, H. J., & Faull, R. L. M. (2013). Striatal parvalbuminergic neurons are lost in Huntington's disease: Implications for dystonia. Movement Disorders, 28(12), 1691–1699. https://doi.org/10.1002/mds.25624

Reiner, A., & Deng, Y. (2018). Disrupted striatal neuron inputs and outputs in Huntington's disease. CNS Neuroscience & Therapeutics, 24(4), 250. https://doi.org/10.1111/CNS.12844

Renoir, T., Pang, T. Y., Zajac, M. S., Chan, G., Du, X., Leang, L., Chevarin, C., Lanfumey, L., & Hannan, A. J. (2012). Treatment of depressive-like behaviour in Huntington's disease mice by chronic sertraline and exercise. British Journal of Pharmacology, 165(5), 1375–1389. https://doi.org/10.1111/J.1476-5381.2011.01567.X

Renoir, T., Zajac, M. S., Du, X., Pang, T. Y., Leang, L., Chevarin, C., Lanfumey, L., & Hannan, A. J. (2011). Sexually Dimorphic Serotonergic Dysfunction in a Mouse Model of Huntington's Disease and Depression. PLOS ONE, 6(7), e22133. https://doi.org/10.1371/JOURNAL.PONE.0022133

Reuter, M. S., Riess, A., Moog, U., Briggs, T. A., Chandler, K. E., Rauch, A., Stampfer, M., Steindl, K., Gläser, D., Joset, P., Krumbiegel, M., Rabe, H., Schulte-Mattler, U., Bauer, P., Beck-Wödl, S., Kohlhase, J., Reis, A., & Zweier, C. (2017). FOXP2 variants in 14 individuals with developmental speech and language disorders broaden the mutational and clinical spectrum. Journal of Medical Genetics, 54(1), 64–72. https://doi.org/10.1136/jmedgenet-2016-104094

Rhijn, J.-R. van, Fisher, S. E., Vernes, S. C., & Kasri, N. N. (2018). Foxp2 loss of function increases striatal direct pathway inhibition via increased GABA release. Brain Structure & Function, 223(9), 4211. https://doi.org/10.1007/S00429-018-1746-6

Ribasés, M., Sánchez-Mora, C., Ramos-Quiroga, J. A., Bosch, R., Gómez, N., Nogueira, M., Corrales, M., Palomar, G., Jacob, C. P., Gross-Lesch, S., Kreiker, S., Reif, A., Lesch, K. P., Cormand, B., Casas, M., & Bayés, M. (2012). An association study of sequence variants in the forkhead box P2 (FOXP2) gene and adulthood attention-deficit/hyperactivity disorder in two European

samples. Psychiatric Genetics, 22(4), 155–160. https://doi.org/10.1097/YPG.0B013E328353957E

Richfield, E. K., O'Brien, C. F., Eskin, T., & Shoulson, I. (1991). Heterogeneous dopamine receptor changes in early and late Huntington's disease. Neuroscience Letters, 132(1), 121–126. https://doi.org/10.1016/0304-3940(91)90448-3

Richfield, E. K., Maguire-Zeiss, K. A., Cox, C., Gilmore, J., & Voorn, P. (1995). Reduced expression of preproenkephalin in striatal neurons from huntington's disease patients. Annals of Neurology, 37(3), 335–343. https://doi.org/10.1002/ANA.410370309

Richter, G., Gui, T., Bourgeois, B., Koyani, C. N., Ulz, P., Heitzer, E., Lewinski, D. von, Burgering, B. M. T., Malle, E., & Madl, T. (2021). β-catenin regulates FOXP2 transcriptional activity via multiple binding sites. The FEBS Journal, 288(10), 3261–3284. https://doi.org/10.1111/FEBS.15656

Rigamonti, D., Bauer, J. H., De-Fraja, C., Conti, L., Sipione, S., Sciorati, C., Clementi, E., Hackam, A., Hayden, M. R., Li, Y., Cooper, J. K., Ross, C. A., Govoni, S., Vincenz, C., & Cattaneo, E. (2000). Wild-type huntingtin protects from apoptosis upstream of caspase-3. Journal of Neuroscience, 20(10), 3705–3713. https://doi.org/10.1523/jneurosci.20-10-03705.2000

Rodenas-Cuadrado, P., Ho, J., & Vernes, S. C. (2013). Shining a light on CNTNAP2: complex functions to complex disorders. European Journal of Human Genetics 2014 22:2, 22(2), 171–178. https://doi.org/10.1038/ejhg.2013.100

Rodrigues, F. B., Abreu, D., Damásio, J., Goncalves, N., Correia-Guedes, L., Coelho, M., & Ferreira, J. J. (2017). Survival, Mortality, Causes and Places of Death in a European Huntington's Disease Prospective Cohort. Movement Disorders Clinical Practice, 4(5), 737–742. https://doi.org/10.1002/MDC3.12502

Rogers, R. D., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999a). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteersEvidence for monoaminergic mechanisms. Neuropsychopharmacology, 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Rogers, R. D., Owen, A. M., Middleton, H. C., Williams, E. J., Pickard, J. D., Sahakian, B. J., & Robbins, T. W. (1999b). Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. Journal of Neuroscience, 19(20), 9029–9038. https://doi.org/10.1523/jneurosci.19-20-09029.1999

Romero, E., Cha, G. H., Verstreken, P., Ly, C. v., Hughes, R. E., Bellen, H. J., & Botas, J. (2008). Suppression of Neurodegeneration and Increased Neurotransmission Caused by Expanded Full-Length Huntingtin Accumulating in the Cytoplasm. Neuron, 57(1), 27–40. https://doi.org/10.1016/J.NEURON.2007.11.025

Roos, R. (2010). Huntington's disease: a clinical review. Orphanet Journal of Rare Diseases, 5(1). https://doi.org/10.1186/1750-1172-5-40

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

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

Rouillon, C., Abraini, J. H., & David, H. N. (2007). Hippocampal modulation of locomotor activity induced by focal activation of postsynaptic dopamine receptors in the core of the nucleus accumbens. Hippocampus, 17(11), 1028–1036. https://doi.org/10.1002/hipo.20337

Rüb, U., Seidel, K., Heinsen, H., Vonsattel, J. P., Dunnen, W. F. den, & Korf, H. W. (2016). Huntington's disease (HD): the neuropathology of a multisystem neurodegenerative disorder of the human brain. Brain Pathology, 26(6), 726. https://doi.org/10.1111/BPA.12426

Rubinsztein, D. C., Leggo, J., Coles, R., Almqvist, E., Biancalana, V., Cassiman, J.-J., Chotai, K., Connarty, M., Craufurd, D., Curtis, A., Curtis, D., Davidson, M. J., Differ, A.-M., Dode, C., Sherr, M., Abbott, M. H., Franz, M. L., Graham, C. A., Harper, P. S., … Hayden, M. R. (1996). Phenotypic Characterization of Individuals with 30-40 CAG Repeats in the Huntington Disease (HD) Gene Reveals HD Cases with 36 Repeats and Apparently Normal Elderly Individuals with 36-39 Repeats. Am. J. Hum. Genet, 59, 16–22.

Rudenko, O., Tkach, V., Berezin, V., & Bock, E. (2009). Detection of early behavioral markers of Huntington's disease in R6/2 mice employing an automated social home cage. Behavioural Brain Research, 203(2), 188–199. https://doi.org/10.1016/J.BBR.2009.04.034

Ruocco, H. H., Lopes-Cendes, I., Li, L. M., & Cendes, F. (2007). Evidence of thalamic dysfunction in Huntington disease by proton magnetic resonance spectroscopy. Movement Disorders, 22(14), 2052–2056. https://doi.org/10.1002/MDS.21601

Saft, C., Schüttke, A., Beste, C., Andrich, J., Heindel, W., & Pfleiderer, B. (2008). fMRI reveals altered auditory processing in manifest and premanifest Huntington's disease. Neuropsychologia, 46(5), 1279–1289. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2007.12.002

Samadi, P., Boutet, A., Rymar, V. v., Rawal, K., Maheux, J., Kvann, J.-C., Tomaszewski, M., Beaubien, F., Cloutier, J. F., Levesque, D., & Sadikot, A. F. (2013). Relationship between BDNF expression in major striatal afferents, striatum morphology and motor behavior in the R6/2 mouse model of Huntington's disease. Genes, Brain and Behavior, 12(1), 108–124. https://doi.org/10.1111/J.1601-183X.2012.00858.X

Sanberg, P. R., Calderon, S. F., Giordano, M., Tew, J. M., & Norman, A. B. (1989). The quinolinic acid model of Huntington's disease: Locomotor abnormalities. Experimental Neurology, 105(1), 45–53. https://doi.org/10.1016/0014-4886(89)90170-2

Sanjuán, J., Tolosa, A., González, J. C., Aguilar, E. J., Pérez-Tur, J., Nájera, C., Moltó, M. D., & Frutos, R. de. (2006). Association between FOXP2 polymorphisms and schizophrenia with auditory hallucinations. Psychiatric Genetics, 16(2), 67–72. https://doi.org/10.1097/01.YPG.0000185029.35558.BB

Sapp, E., Penney, J., Young, A., Aronin, N., Vonsattel, J. P., & DiFiglia, M. (1999). Axonal transport of N-terminal huntingtin suggests early pathology of corticostriatal projections in huntington disease. Journal of Neuropathology and Experimental Neurology, 58(2), 165–173. https://doi.org/10.1097/00005072-199902000-00006

Sapp, E., Seeley, C., Iuliano, M., Weisman, E., Vodicka, P., DiFiglia, M., & Kegel-Gleason, K. B. (2020). Protein changes in synaptosomes of Huntington's disease knock-in mice are dependent on age and brain region. Neurobiology of Disease, 141, 104950. https://doi.org/10.1016/J.NBD.2020.104950

Say, M. J., Jones, R., Scahill, R. I., Dumas, E. M., Coleman, A., Santos, R. C. D., Justo, D., Campbell, J. C., Queller, S., Shores, E. A., Tabrizi, S. J., & Stout, J. C. (2011). Visuomotor integration

deficits precede clinical onset in Huntington's disease. Neuropsychologia, 49(2), 264–270. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2010.11.016

Schaffar, G., Breuer, P., Boteva, R., Behrends, C., Tzvetkov, N., Strippel, N., Sakahira, H., Siegers, K., Hayer-Hartl, M., & Hartl, F. U. (2004). Cellular toxicity of polyglutamine expansion proteins: Mechanism of transcription factor deactivation. Molecular Cell, 15(1), 95–105. https://doi.org/10.1016/j.molcel.2004.06.029

Schilling, G., Becher, M. W., Sharp, A. H., Jinnah, H. A., Duan, K., Kotzuk, J. A., Slunt, H. H., Ratovitski, T., Cooper, J. K., Jenkins, N. A., Copeland, N. G., Price, D. L., Ross, C. A., & Borchelt, D. R. (1999). Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Human Molecular Genetics, 8(3), 397–407. https://doi.org/10.1093/hmg/8.3.397

Schippling, S., Schneider, S. A., Bhatia, K. P., Münchau, A., Rothwell, J. C., Tabrizi, S. J., & Orth, M. (2009). Abnormal Motor Cortex Excitability in Preclinical and Very Early Huntington's Disease. Biological Psychiatry, 65(11), 959–965. https://doi.org/10.1016/J.BIOPSYCH.2008.12.026

Schoenfeld, M., Myers, R. H., Cupples, L. A., Berkman, B., Sax, D. S., & Clark, E. (1984). Increased rate of suicide among patients with Huntington's disease. Neurosurgery, and Psychiatry, 47, 1283–1287. https://doi.org/10.1136/jnnp.47.12.1283

Schroeder, D. I., & Myers, R. M. (2008). Multiple transcription start sites for FOXP2 with varying cellular specificities. Gene, 413(1–2), 42–48. https://doi.org/10.1016/j.gene.2008.01.015

Schulz, S. B., Haesler, S., Scharff, C., & Rochefort, C. (2010). Knockdown of FoxP2 alters spine density in Area X of the zebra finch. Genes, Brain and Behavior, 9(7), 732–740. https://doi.org/10.1111/J.1601-183X.2010.00607.X

Schultz, J. L., Kamholz, J. A., Moser, D. J., Feely, S. M. E., Paulsen, J. S., & Nopoulos, P. C. (2017). Substance abuse may hasten motor onset of Huntington disease: Evaluating the Enroll-HD database. Neurology, 88(9), 909. https://doi.org/10.1212/WNL.0000000000003661

Schwarcz, R., Whetsell, W. O., & Mangano, R. M. (1983). Quinolinic acid: An endogenous metabolite that produces axon-sparing lesions in rat brain. Science, 219(4582), 316–318. https://doi.org/10.1126/science.6849138

Schwartz, W. J., & Zimmerman, P. (1991). Lesions of the suprachiasmatic nucleus disrupt circadian locomotor rhythms in the mouse. Physiology & Behavior, 49(6), 1283–1287. https://doi.org/10.1016/0031-9384(91)90364-T

Scott, R., Sánchez-Aguilera, A., van Elst, K., Lim, L., Dehorter, N., Bae, S. E., Bartolini, G., Peles, E., Kas, M. J. H., Bruining, H., & Marín, O. (2019). Loss of Cntnap2 Causes Axonal Excitability Deficits, Developmental Delay in Cortical Myelination, and Abnormal Stereotyped Motor Behavior. Cerebral Cortex, 29(2), 586–597. https://doi.org/10.1093/cercor/bhx341

Selden, N., Geula, C., Hersh, L., & Mesulam, M. M. (1994). Human striatum: Chemoarchitecture of the caudate nucleus, putamen and ventral striatum in health and Alzheimer's disease. Neuroscience, 60(3), 621–636. https://doi.org/10.1016/0306-4522(94)90491-X

Selkoe, D. J. (2002). Alzheimer's disease is a synaptic failure. Science, 298(5594), 789–791. https://doi.org/10.1126/SCIENCE.1074069

Seppi, K., Mueller, J., Bodner, T., Brandauer, E., Benke, T., Weirich-Schwaiger, H., Poewe, W., & Wenning, G. K. (2001). Riluzole in Huntington's disease (HD): An open label study with one year follow up. Journal of Neurology, 248(10), 866–869. https://doi.org/10.1007/s004150170071

Shehadeh, HB, F., MM, Z. M., RK, G., BR, L., MR, H., & LA, R. (2006). Striatal neuronal apoptosis is preferentially enhanced by NMDA receptor activation in YAC transgenic mouse model of Huntington disease. Neurobiology of Disease, 21(2), 392–403. https://doi.org/10.1016/J.NBD.2005.08.001

Shelbourne, P. F., Killeen, N., Hevner, R. F., Johnston, H. M., Tecott, L., Lewandoski, M., Ennis, M., Ramirez, L., Li, Z., Iannicola, C., Littman, D. R., & Myers, R. M. (1999). A Huntington's Disease CAG Expansion at the Murine Hdh Locus Is Unstable and Associated with Behavioural Abnormalities in Mice. Human Molecular Genetics, 8(5), 763–774. https://doi.org/10.1093/HMG/8.5.763

Shepherd. (2013). Corticostriatal connectivity and its role in disease. Nature Reviews. Neuroscience, 14(4), 278–291. https://doi.org/10.1038/NRN3469

Shimojo, M. (2008). Huntingtin regulates RE1-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) nuclear trafficking indirectly through a complex with REST/NRSF-interacting LIM domain protein (RILP) and dynactin p150 Glued. Journal of Biological Chemistry, 283(50), 34880–34886. https://doi.org/10.1074/jbc.M804183200

Shu, W., Yang, H., Zhang, L., Lu, M. M., & Morrisey, E. E. (2001). Characterization of a New Subfamily of Winged-helix/Forkhead (Fox) Genes That Are Expressed in the Lung and Act as Transcriptional Repressors *. Journal of Biological Chemistry, 276(29), 27488–27497. https://doi.org/10.1074/JBC.M100636200

Shu, W., Cho, J. Y., Jiang, Y., Zhang, M., Weisz, D., Elder, G. A., Schmeidler, J., Gasperi, R. de, Sosa, M. A. G., Rabidou, D., Santucci, A. C., Perl, D., Morrisey, E., & Buxbaum, J. D. (2005). Altered ultrasonic vocalization in mice with a disruption in the Foxp2 gene. Proceedings of the National Academy of Sciences of the United States of America, 102(27), 9643. https://doi.org/10.1073/PNAS.0503739102

Siavash, F. D., Schwartz, S. E. R., Qihao, Q., Rinaldo, C.-P., Lin-Ling, P. E., Mandell, J. D., Amanda, E., Anna, R., Rebecca, Krasnoff, A., Sol, K., David, T., Nord, A. S., Jeremy, W. A., Bin, C., State, M. W., Sohal, V. S., & Rubenstein, J. L. R. (2018). Neonatal Tbr1 Dosage Controls Cortical Layer 6 Connectivity. Neuron, 100(4), 831. https://doi.org/10.1016/J.NEURON.2018.09.027

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., … von Hörsten, S. (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 of the United States of America, 115(37), E8765–E8774. https://doi.org/10.1073/pnas.1807962115

Siegel, A., Roeling, T. A. P., Gregg, T. R., & Kruk, M. R. (1999). Neuropharmacology of brain-stimulation-evoked aggression. Neuroscience & Biobehavioral Reviews, 23(3), 359–389. https://doi.org/10.1016/S0149-7634(98)00040-2

Silva, F. R., Miranda, A. S., Santos, R. P. M., Olmo, I. G., Zamponi, G. W., Dobransky, T., Cruz, J. S., Vieira, L. B., & Ribeiro, F. M. (2017). N-type Ca2+ channels are affected by full-length mutant huntingtin expression in a mouse model of Huntington's disease. Neurobiology of Aging, 55, 1–10. https://doi.org/10.1016/J.NEUROBIOLAGING.2017.03.015

Simon, N. W., Beas, B. S., Montgomery, K. S., Haberman, R. P., Bizon, J. L., & Setlow, B. (2013). Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. European Journal of Neuroscience, 37(11), 1779–1788. https://doi.org/10.1111/ejn.12191

Simmons, D. A., Belichenko, N. P., Ford, E. C., Semaan, S., Monbureau, M., Aiyaswamy, S., Holman, C. M., Condon, C., Shamloo, M., Massa, S. M., & Longo, F. M. (2016). A small molecule p75NTR ligand normalizes signalling and reduces Huntington's disease phenotypes in R6/2 and BACHD mice. Human Molecular Genetics, 25(22), 4920–4938. https://doi.org/10.1093/HMG/DDW316

Simmons, D. A. (2017). Modulating Neurotrophin Receptor Signaling as a Therapeutic Strategy for Huntington's Disease. Journal of Huntington's Disease, 6(4), 303–325. https://doi.org/10.3233/JHD-170275

Sipione, S., Rigamonti, D., Valenza, M., Zuccato, C., Conti, L., Pritchard, J., Kooperberg, C., Olson, J. M., & Cattaneo, E. (2002). Early transcriptional profiles in huntingtin-inducible striatal cells by microarray analyses. Human Molecular Genetics, 11(17), 1953–1965. https://doi.org/10.1093/HMG/11.17.1953

Skillings, E. A., Wood, N. I., & Morton, A. J. (2014). Beneficial effects of environmental enrichment and food entrainment in the R6/2 mouse model of Huntington's disease. Brain and Behavior, 4(5), 675–686. https://doi.org/10.1002/BRB3.235

Slaughter, J. R., Martens, M. P., & Slaughter, K. A. (2001). Depression and Huntington's disease: Prevalence, clinical manifestations, etiology, and treatment. CNS Spectrums, 6(4), 306–326. https://doi.org/10.1017/s109285290002201x

Slow, E. J., van Raamsdonk, J., Rogers, D., Coleman, S. H., Graham, R. K., Deng, Y., Oh, R., Bissada, N., Hossain, S. M., Yang, Y. Z., Li, X. J., Simpson, E. M., Gutekunst, C. A., Leavitt, B. R., & Hayden, M. R. (2003). Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. In Human Molecular Genetics (Vol. 12, Issue 13, pp. 1555–1567). Hum Mol Genet. https://doi.org/10.1093/hmg/ddg169

Smarr, B., Cutler, T., Loh, D. H., Kudo, T., Kuljis, D., Kriegsfeld, L., Ghiani, C. A., & Colwell, C. S. (2019). Circadian dysfunction in the Q175 model of Huntington's disease: network analysis. Journal of Neuroscience Research, 97(12), 1606. https://doi.org/10.1002/JNR.24505

Smith, Mowery, T. M., & Alloway, K. D. (2012). Thalamic POm projections to the dorsolateral striatum of rats: potential pathway for mediating stimulus–response associations for sensorimotor habits. Https://Doi.Org/10.1152/Jn.00142.2012, 108(1), 160–174. https://doi.org/10.1152/JN.00142.2012

Smith, R., Brundin, P., & Li, J.-Y. (2005). Synaptic dysfunction in Huntington's disease: a new perspective. Cellular and Molecular Life Sciences, 62(17), 1901–1912. https://doi.org/10.1007/s00018-005-5084-5

Smith, R., Petersén, Å., Bates, G. P., Brundin, P., & Li, J. Y. (2005). Depletion of rabphilin 3A in a transgenic mouse model (R6/1) of Huntington's disease, a possible culprit in synaptic dysfunction. Neurobiology of Disease, 20(3), 673–684. https://doi.org/10.1016/J.NBD.2005.05.008

Smith, Y., Raju, D. v., Pare, J. F., & Sidibe, M. (2004). The thalamostriatal system: a highly specific network of the basal ganglia circuitry. Trends in Neurosciences, 27(9), 520–527. https://doi.org/10.1016/J.TINS.2004.07.004

Smith, Y., Galvan, A., Ellender, T. J., Doig, N., Villalba, R. M., Ocampo, I. H., Wichman, T., & Bolam, P. (2014). The thalamostriatal system in normal and diseased states. Frontiers in Systems Neuroscience, 0(JAN), 5. https://doi.org/10.3389/FNSYS.2014.00005

Smith-Dijak, A. I., Sepers, M. D., & Raymond, L. A. (2019). Alterations in synaptic function and plasticity in Huntington disease. Journal of Neurochemistry, 150(4), 346–365. https://doi.org/10.1111/JNC.14723

Soderstrom, H., Hultin, L., Tullberg, M., Wikkelso, C., Ekholm, S., & Forsman, A. (2002). Reduced frontotemporal perfusion in psychopathic personality. Psychiatry Research - Neuroimaging, 114(2), 81–94. https://doi.org/10.1016/S0925-4927(02)00006-9

Solberg, O. K., Filkuková, P., Frich, J. C., & Feragen, K. J. B. (2018). Age at Death and Causes of Death in Patients with Huntington Disease in Norway in 1986–2015. Journal of Huntington's Disease, 7(1), 77. https://doi.org/10.3233/JHD-170270

Soler Artigas, M., Sánchez-Mora, C., Rovira, P., Richarte, V., Garcia-Martínez, I., Pagerols, M., Demontis, D., Stringer, S., Vink, J. M., Børglum, A. D., Neale, B. M., Franke, B., Faraone, S. v., Casas, M., Ramos-Quiroga, J. A., & Ribasés, M. (2019). Attention-deficit/hyperactivity disorder and lifetime cannabis use: genetic overlap and causality. Molecular Psychiatry. https://doi.org/10.1038/s41380-018-0339-3

Sotrel, A., Paskevich, P. A., Kiely, D. K., Bird, E. D., Williams, R. S., & Myers, R. H. (1991). Morphometric analysis of the prefrontal cortex in huntington's disease. Neurology, 41(7), 1117–1123. https://doi.org/10.1212/wnl.41.7.1117

Španiel, F., Horáček, J., Tintěra, J., Ibrahim, I., Novák, T., Čermák, J., Klírová Monika, M., & Höschl, C. (2011). Genetic variation in FOXP2 alters grey matter concentrations in schizophrenia patients. Neuroscience Letters, 493(3), 131–135. https://doi.org/10.1016/J.NEULET.2011.02.024

Spires, T. L., Grote, H. E., Garry, S., Cordery, P. M., van Dellen, A., Blakemore, C., & Hannan, A. J. (2004). Dendritic spine pathology and deficits in experience-dependent dendritic plasticity in R6/1 Huntington's disease transgenic mice. European Journal of Neuroscience, 19(10), 2799–2807. https://doi.org/10.1111/J.0953-816X.2004.03374.X

Spiteri, E., Konopka, G., Coppola, G., Bomar, J., Oldham, M., Ou, J., Vernes, S. C., Fisher, S. E., Ren, B., & Geschwind, D. H. (2007). Identification of the Transcriptional Targets of FOXP2, a Gene Linked to Speech and Language, in Developing Human Brain. The American Journal of Human Genetics, 81(6), 1144–1157. https://doi.org/10.1086/522237

Spokes, E. G. S. (1980). Neurochemical alterations in huntington's choreaa study of post-mortem brain tissue. Brain, 103(1), 179–210. https://doi.org/10.1093/BRAIN/103.1.179

Squitieri, F., Cannella, M., Simonelli, M., Sassone, J., Martino, T., Venditti, E., Ciammola, A., Colonnese, C., Frati, L., & Ciarmiello, A. (2009). Distinct brain volume changes correlating with clinical stage, disease progression rate, mutation size, and age at onset prediction as early biomarkers of brain atrophy in Huntington's disease. CNS Neuroscience and Therapeutics, 15(1), 1–11. https://doi.org/10.1111/j.1755-5949.2008.00068.x

St Clair, D., Blackwood, D., Muir, W., Walker, M., St Clair, D., Muir, W., Carothers, A., Spowart, G., Gosden, C., & Evans, H. J. (1990). Association within a family of a balanced autosomal translocation with major mental illness. The Lancet, 336(8706), 13–16. https://doi.org/10.1016/0140-6736(90)91520-K

Stack, E. C., Kubilus, J. K., Smith, K., Cormier, K., del Signore, S. J., Guelin, E., Ryu, H., Hersch, S. M., & Ferrante, R. J. (2005). Chronology of behavioral symptoms and neuropathological sequela in R6/2 Huntington's disease transgenic mice. Journal of Comparative Neurology, 490(4), 354–370. https://doi.org/10.1002/cne.20680

REFERENCES

Standaert, D. G. (1999). NMDA receptors and nitric oxide synthase. Molecular Psychiatry, 4(1), 13–14. https://doi.org/10.1038/SJ.MP.4000437

Steele, J. S., Bertocci, M., Eckstrand, K., Chase, H. W., Stiffler, R., Aslam, H., Lockovich, J., Bebko, G., & Phillips, M. L. (2021). A specific neural substrate predicting current and future impulsivity in young adults. Molecular Psychiatry 2021, 1–12. https://doi.org/10.1038/s41380-021-01017-0

Steffan, J. S., Bodai, L., Pallos, J., Poelman, M., McCampbell, A., Apostol, B. L., Kazantsev, A., Schmidt, E., Zhu, Y. Z., Greenwald, M., Kurokawa, R., Housman, D. E., Jackson, G. R., Marsh, J. L., & Thompson, L. M. (2001). Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature, 413(6857), 739–743. https://doi.org/10.1038/35099568

Steffan, J. S., Kazantsev, A., Spasic-Boskovic, O., Greenwald, M., Zhu, Y.-Z., Gohler, H., Wanker, E. E., Bates, G. P., Housman, D. E., & Thompson, L. M. (2000). The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proceedings of the National Academy of Sciences, 97(12), 6763–6768. https://doi.org/10.1073/PNAS.100110097

Stern. (2011). Functional Changes in Neocortical Activity in Huntington's Disease Model Mice: An in vivo Intracellular Study. Frontiers in Systems Neuroscience, 5(JUNE 2011). https://doi.org/10.3389/FNSYS.2011.00047

Steventon, J. J., Trueman, R. C., Ma, D., Yhnell, E., Bayram-Weston, Z., Modat, M., Cardoso, J., Ourselin, S., Lythgoe, M., Stewart, A., Rosser, A. E., & Jones, D. K. (2016). Longitudinal in vivo MRI in a Huntington's disease mouse model: Global atrophy in the absence of white matter microstructural damage. Scientific Reports 2016 6:1, 6(1), 1–12. https://doi.org/10.1038/srep32423

Strauss, K. A., Puffenberger, E. G., Huentelman, M. J., Gottlieb, S., Dobrin, S. E., Parod, J. M., Stephan, D. A., & Morton, D. H. (2009). Recessive Symptomatic Focal Epilepsy and Mutant Contactin-Associated Protein-like 2. Http://Dx.Doi.Org/10.1056/NEJMoa052773, 354(13), 1370–1377. https://doi.org/10.1056/NEJMOA052773

Strawbridge, R. J., Ward, J., Lyall, L. M., Tunbridge, E. M., Cullen, B., Graham, N., Ferguson, A., Johnston, K. J. A., Lyall, D. M., Mackay, D., Cavanagh, J., Howard, D. M., Adams, M. J., Deary, I., Escott-Price, V., O'Donovan, M., McIntosh, A. M., Bailey, M. E. S., Pell, J. P., … Smith, D. J. (2018). Genetics of self-reported risk-taking behaviour, trans-ethnic consistency and relevance to brain gene expression. Translational Psychiatry, 8(1). https://doi.org/10.1038/s41398-018-0236-1

Sturman, O., Germain, P. L., & Bohacek, J. (2018). Exploratory rearing: a context- and stress-sensitive behavior recorded in the open-field test. Stress, 21(5), 443–452. https://doi.org/10.1080/10253890.2018.1438405

Suelves, N., Kirkham-McCarthy, L., Lahue, R. S., & Ginés, S. (2017). A selective inhibitor of histone deacetylase 3 prevents cognitive deficits and suppresses striatal CAG repeat expansions in Huntington's disease mice. Scientific Reports, 7(1). https://doi.org/10.1038/S41598-017-05125-2

Sugiyama, M., Nishijima, I., Miyazaki, S., & Nakamura, T. J. (2020). Secretin receptor-deficient mice exhibit altered circadian rhythm in wheel-running activity. Neuroscience Letters, 722. https://doi.org/10.1016/J.NEULET.2020.134814

Sun, Y., Savanenin, A., Reddy, P. H., & Liu, Y. F. (2001). Polyglutamine-expanded Huntingtin Promotes Sensitization of N-Methyl-D-aspartate Receptors via Post-synaptic Density 95. Journal of Biological Chemistry, 276(27), 24713–24718. https://doi.org/10.1074/jbc.M103501200

Suzuki, TJ, D., RL, A., & KA, F. (2001). Vesicular neurotransmitter transporters in Huntington's disease: initial observations and comparison with traditional synaptic markers. Synapse (New York, N.Y.), 41(4), 329–336. https://doi.org/10.1002/SYN.1089

Swayne, L. A., Chen, L., Hameed, S., Barr, W., Charlesworth, E., Colicos, M. A., Zamponi, G. W., & Braun, J. E. A. (2005). Crosstalk between huntingtin and syntaxin 1A regulates N-type calcium channels. Molecular and Cellular Neuroscience, 30(3), 339–351. https://doi.org/10.1016/J.MCN.2005.07.016

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., Scahill, R. I., Durr, A., Roos, R. A. C., 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

Taepavarapruk, P., Floresco, S. B., & Phillips, A. G. (2000). Hyperlocomotion and increased dopamine efflux in the rat nucleus accumbens evoked by electrical stimulation of the ventral subiculum: role of ionotropic glutamate and dopamine D1 receptors. Psychopharmacology 2000 151:2, 151(2), 242–251. https://doi.org/10.1007/S002130000376

Takano, H., & Gusella, J. F. (2002). The predominantly HEAT-like motif structure of huntingtin and its association and coincident nuclear entry with dorsal, an NF-kB/Rel/dorsal family transcription factor. BMC Neuroscience, 3. https://doi.org/10.1186/1471-2202-3-15

Takahashi, K., Liu, F. C., Hirokawa, K., & Takahashi, H. (2003). Expression of Foxp2, a gene involved in speech and language, in the developing and adult striatum. Journal of Neuroscience Research, 73(1), 61–72. https://doi.org/10.1002/jnr.10638

Tartari, M., Gissi, C., lo Sardo, V., Zuccato, C., Picardi, E., Pesole, G., & Cattaneo, E. (2008). Phylogenetic Comparison of Huntingtin Homologues Reveals the Appearance of a Primitive polyQ in Sea Urchin. Molecular Biology and Evolution, 25(2), 330–338. https://doi.org/10.1093/MOLBEV/MSM258

Tasaki, Y., Makino, Y., Ohta, S., & Hirobe, M. (1991). 1-Methyl- 1,2,3,4-Tetrahydroisoquinoline, Decreasing in 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Treated Mouse, Prevents Parkinsonism-Like Behavior Abnormalities. Journal of Neurochemistry, 57(6), 1940–1943. https://doi.org/10.1111/j.1471-4159.1991.tb06407.x

Taylor-Robinson, S. D., Weeks, R. A., Bryant, D. J., Sargentoni, J., Marcus, C. D., Harding, A. E., & Brooks, D. J. (1996). Proton magnetic resonance spectroscopy in Huntington's disease: Evidence in favour of the glutamate excitotoxic theory? Movement Disorders, 11(2), 167–173. https://doi.org/10.1002/MDS.870110209

Tedford, S. E., Persons, A. L., & Napier, T. C. (2015). Dopaminergic Lesions of the Dorsolateral Striatum in Rats Increase Delay Discounting in an Impulsive Choice Task. PLOS ONE, 10(4), e0122063. https://doi.org/10.1371/JOURNAL.PONE.0122063

The Huntington's Disease Collaborative Research Group. (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

The Huntington Study, G. (2001). A randomized, placebo-controlled trial of coenzyme Q 10 and remacemide in Huntington's disease. Neurology, 57(3), 397.1-404. https://doi.org/10.1212/wnl.57.3.397

Telenius, H., Kremer, H. P. H., Thellmann, J., Andrew, S. E., Almqvist, E., Anvret, M., Greenberg, C., Greenberg, J., Lucotte, G., Squltierl, F., Starr, A., Goldberg, Y. P., & Hayden, M. R. (1993). Molecular analysis of juvenile huntington disease: The major influence on (CAG)n repeat length is the sex of the affected parent. Human Molecular Genetics, 2(10), 1535–1540. https://doi.org/10.1093/hmg/2.10.1535

Teramitsu, I., Kudo, L. C., London, S. E., Geschwind, D. H., & White, S. A. (2004). Parallel FoxP1 and FoxP2 Expression in Songbird and Human Brain Predicts Functional Interaction. The Journal of Neuroscience, 24(13), 3152. https://doi.org/10.1523/JNEUROSCI.5589-03.2004

Tepper, J. M., Koós, T., & Wilson, C. J. (2004). GABAergic microcircuits in the neostriatum. In Trends in Neurosciences (Vol. 27, Issue 11, pp. 662–669). Trends Neurosci. https://doi.org/10.1016/j.tins.2004.08.007

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. Https://Doi.Org/10.1176/Appi.Neuropsych.11030057, 24(1), 53–60. https://doi.org/10.1176/APPI.NEUROPSYCH.11030057

Thulo, M., Rabie, M. A., Pahad, N., Donald, H. L., Blane, A. A., Perumal, C. M., Penedo, J. C., & Fanucchi, S. (2021). The influence of various regions of the FOXP2 sequence on its structure and DNA-binding function. Bioscience Reports, 41(1). https://doi.org/10.1042/BSR20202128

Tiihonen, J., Kuikka, J., Bergström, K., Hakola, P., Karhu, J., Ryynänen, O. P., & Föhr, J. (1995). Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. Nature Medicine, 1(7), 654–657. https://doi.org/10.1038/nm0795-654

Tolosa, A., Sanjuán, J., Dagnall, A. M., Moltó, M. D., Herrero, N., & de Frutos, R. (2010). FOXP2 gene and language impairment in schizophrenia: Association and epigenetic studies. BMC Medical Genetics, 11(1). https://doi.org/10.1186/1471-2350-11-114

Tornero, D., Tsupykov, O., Granmo, M., Rodriguez, C., Grønning-Hansen, M., Thelin, J., Smozhanik, E., Laterza, C., Wattananit, S., Ge, R., Tatarishvili, J., Grealish, S., Brüstle, O., Skibo, G., Parmar, M., Schouenborg, J., Lindvall, O., & Kokaia, Z. (2017). Synaptic inputs from stroke-injured brain to grafted human stem cell-derived neurons activated by sensory stimuli. Brain, 140(3), 692–706. https://doi.org/10.1093/BRAIN/AWW347

Trottier, Y., Biancalana, V., & Mandel, J. L. (1994). Instability of CAG repeats in Huntington's disease: Relation to parental transmission and age of onset. Journal of Medical Genetics, 31(5), 377–382. https://doi.org/10.1136/jmg.31.5.377

Tsui, D., Vessey, J. P., Tomita, H., Kaplan, D. R., & Miller, F. D. (2013). FoxP2 Regulates Neurogenesis during Embryonic Cortical Development. The Journal of Neuroscience, 33(1), 244. https://doi.org/10.1523/JNEUROSCI.1665-12.2013

Turner, R. S., & Desmurget, M. (2010). Basal Ganglia Contributions to Motor Control: A Vigorous Tutor. Current Opinion in Neurobiology, 20(6), 704. https://doi.org/10.1016/J.CONB.2010.08.022

Turrigiano, G. (2012). Homeostatic Synaptic Plasticity: Local and Global Mechanisms for Stabilizing Neuronal Function. Cold Spring Harbor Perspectives in Biology, 4(1). https://doi.org/10.1101/CSHPERSPECT.A005736

Unschuld, P. G., Joel, S. E., Liu, X., Shanahan, M., Margolis, R. L., Biglan, K. M., Bassett, S. S., Schretlen, D. J., Redgrave, G. W., van Zijl, P. C. M., Pekar, J. J., & Ross, C. A. (2012). Impaired cortico-striatal functional connectivity in prodromal Huntington's Disease. Neuroscience Letters, 514(2), 204–209. https://doi.org/10.1016/J.NEULET.2012.02.095

Usdin, M. T., Shelbourne, P. F., Myers, R. M., & Madison, D. v. (1999). Impaired Synaptic Plasticity in Mice Carrying the Huntington's Disease Mutation. Human Molecular Genetics, 8(5), 839–846. https://doi.org/10.1093/HMG/8.5.839

Valencia, A., Sapp, E., Kimm, J. S., McClory, H., Ansong, K. A., Yohrling, G., Kwak, S., Kegel, K. B., Green, K. M., Shaffer, S. A., Aronin, N., & DiFiglia, M. (2013). Striatal synaptosomes from Hdh140Q/140Q knock-in mice have altered protein levels, novel sites of methionine oxidation, and excess glutamate release after stimulation. Journal of Huntington's Disease, 2(4), 459–475. https://doi.org/10.3233/JHD-130080

Valor, L. M., & Guiretti, D. (2014). What's wrong with epigenetics in Huntington's disease? Neuropharmacology, 80, 103–114. https://doi.org/10.1016/J.NEUROPHARM.2013.10.025

van Dellen, A., Blakemore, C., Deacon, R., York, D., & Hannan, A. J. (2000). Delaying the onset of Huntington's in mice. Nature 2000 404:6779, 404(6779), 721–722. https://doi.org/10.1038/35008142

van Dellen, A., Welch, J., Dixon, R. M., Cordery, P., York, D., Styles, P., Blakemore, C., & Hannan, A. J. (2000). N-Acetylaspartate and DARPP-32 levels decrease in the corpus striatum of Huntington's disease mice. NeuroReport, 11(17), 3751–3757. https://doi.org/10.1097/00001756-200011270-00032

van der Loos, H. (1976). Barreloids in mouse somatosensory thalamus. Neuroscience Letters, 2(1), 1–6. https://doi.org/10.1016/0304-3940(76)90036-7

van Raamsdonk, J. M., Murphy, Z., Slow, E. J., Leavitt, B. R., & Hayden, M. R. (2005). Selective degeneration and nuclear localization of mutant huntingtin in the YAC128 mouse model of Huntington disease. Human Molecular Genetics, 14(24), 3823–3835. https://doi.org/10.1093/HMG/DDI407

van Rhijn, J. R., Fisher, S. E., Vernes, S. C., & Nadif Kasri, N. (2018). Foxp2 loss of function increases striatal direct pathway inhibition via increased GABA release. Brain Structure and Function, 223(9), 4211–4226. https://doi.org/10.1007/s00429-018-1746-6

Vandamme, T. F. (2014). Use of rodents as models of human diseases. Journal of Pharmacy & Bioallied Sciences, 6(1), 2. https://doi.org/10.4103/0975-7406.124301

Vargha-Khadem, F., Watkins, K., Alcock, K., Fletcher, P., & Passingham, R. (1995). Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. Proceedings of the National Academy of Sciences, 92(3), 930–933. https://doi.org/10.1073/PNAS.92.3.930

Vargha-Khadem, F., Watkins, K. E., Price, C. J., Ashburner, J., Alcock, K. J., Connelly, A., Frackowiak, R. S. J., Friston, K. J., Pembrey, M. E., Mishkin, M., Gadian, D. G., & Passingham,

R. E. (1998). Neural basis of an inherited speech and language disorder. Proceedings of the National Academy of Sciences, 95(21), 12695–12700. https://doi.org/10.1073/PNAS.95.21.12695

Velier, J., Kim, M., Schwarz, C., Kim, T. W., Sapp, E., Chase, K., Aronin, N., & DiFiglia, M. (1998). Wild-type and mutant huntingtins function in vesicle trafficking in the secretory and endocytic pathways. Experimental Neurology, 152(1), 34–40. https://doi.org/10.1006/exnr.1998.6832

Verdin, E., & Ott, M. (2014). 50 years of protein acetylation: from gene regulation to epigenetics, metabolism and beyond. Nature Reviews Molecular Cell Biology 2014 16:4, 16(4), 258–264. https://doi.org/10.1038/nrm3931

Vernes, S. C., Newbury, D. F., Abrahams, B. S., Winchester, L., Nicod, J., Groszer, M., Alarcón, M., Oliver, P. L., Davies, K. E., Geschwind, D. H., Monaco, A. P., & Fisher, S. E. (2008). A Functional Genetic Link between Distinct Developmental Language Disorders. New England Journal of Medicine, 359(22), 2337–2345. https://doi.org/10.1056/nejmoa0802828

Vernes, S. C., Oliver, P. L., Spiteri, E., Lockstone, H. E., Puliyadi, R., Taylor, J. M., Ho, J., Mombereau, C., Brewer, A., Lowy, E., Nicod, J., Groszer, M., Baban, D., Sahgal, N., Cazier, J. B., Ragoussis, J., Davies, K. E., Geschwind, D. H., & Fisher, S. E. (2011). FOXP2 regulates gene networks implicated in neurite outgrowth in the developing brain. PLoS Genetics, 7(7). https://doi.org/10.1371/journal.pgen.1002145

Vonsattel, J. P., Myers, R. H., Stevens, T. J., Ferrante, R. J., Bird, E. D., & Richardson, E. P. (1985). Neuropathological classification of huntington's disease. Journal of Neuropathology and Experimental Neurology, 44(6), 559–577. https://doi.org/10.1097/00005072-198511000-00003

Vonsattel, J. P. G., & Difiglia, M. (1998). Huntington Disease. Journal of Neuropathology & Experimental Neurology, 57(5), 369–384. https://doi.org/10.1097/00005072-199805000-00001

Vonsattel, J. P. G., Keller, C., & Pilar Amaya, M. del. (2008). Neuropathology of Huntington's Disease. In Handbook of Clinical Neurology (Vol. 89, pp. 599–618). Elsevier. https://doi.org/10.1016/S0072-9752(07)01256-0

Vonsattel, J. P. G., Keller, C., & Cortes Ramirez, E. P. (2011). Huntington's disease - neuropathology. In Handbook of Clinical Neurology (Vol. 100, pp. 83–100). Elsevier. https://doi.org/10.1016/B978-0-444-52014-2.00004-5

Waldvogel, H. J., Kim, E. H., Tippett, L. J., Vonsattel, J. P. G., & Faull, R. L. M. (2014). The neuropathology of Huntington's disease. Current Topics in Behavioral Neurosciences, 22, 33–80. https://doi.org/10.1007/7854_2014_354

Walker, A. G., Miller, B. R., Fritsch, J. N., Barton, S. J., & Rebec, G. v. (2008). Altered information processing in the prefrontal cortex of Huntington's disease mouse models. Journal of Neuroscience, 28(36), 8973–8982. https://doi.org/10.1523/JNEUROSCI.2804-08.2008

Walker, F. O. (2007). Huntington's disease. The Lancet, 369(9557), 218–228. https://doi.org/10.1016/S0140-6736(07)60111-1

Walker, R. M., Hill, A. E., Newman, A. C., Hamilton, G., Torrance, H. S., Anderson, S. M., Ogawa, F., Derizioti, P., Nicod, J., Vernes, S. C., Fisher, S. E., Thomson, P. A., Porteous, D. J., & Evans, K. L. (2012). The DISC1 promoter: Characterization and regulation by FOXP2. Human Molecular Genetics, 21(13), 2862–2872. https://doi.org/10.1093/hmg/dds111

Wang, H., del Mar, N., Deng, Y., & Reiner, A. (2021). Rescue of BDNF expression by the thalamic parafascicular nucleus with chronic treatment with the mGluR2/3 agonist LY379268 may contribute to the LY379268 rescue of enkephalinergic striatal projection neurons in R6/2 Huntington's disease mice. Neuroscience Letters, 763, 136180. https://doi.org/10.1016/J.NEULET.2021.136180

Weeks, R. A., Piccini, P., Harding, A. E., & Brooks, D. J. (1996). Striatal D1 and D2 dopamine receptor loss in asymptomatic mutation carriers of Huntington's disease. Annals of Neurology, 40(1), 49–54. https://doi.org/10.1002/ANA.410400110

Wetzel, H. H., Gehl, C. R., Dellefave, L., Schiffman, J. F., Shannon, K. M., Paulsen, J. S., & Group, H. S. (2011). Suicidal ideation in Huntington disease: The role of comorbidity. Psychiatry Research, 188(3), 372. https://doi.org/10.1016/J.PSYCHRES.2011.05.006

Wexler, N. S., Lorimer, J., Porter, J., Gomez, F., Moskowitz, C., Shackell, E., Marder, K., Penchaszadeh, G., Roberts, S. A., Gayán, J., Brocklebank, D., Cherny, S. S., Cardon, L. R., Gray, J., Dlouhy, S. R., Wiktorski, S., Hodes, M. E., Conneally, P. M., Penney, J. B., … Landwehrmeyeri, B. (2004). Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proceedings of the National Academy of Sciences of the United States of America, 101(10), 3498–3503. https://doi.org/10.1073/pnas.0308679101

Wheeler, V. C., Auerbach, W., White, J. K., Srinidhi, J., Auerbach, A., Ryan, A., Duyao, M. P., Vrbanac, V., Weaver, M., Gusella, J. F., Joyner, A. L., & MacDonald, M. E. (1999). Length-dependent gametic CAG repeat instability in the Huntington's disease knock-in mouse. Human Molecular Genetics, 8(1), 115–122. https://doi.org/10.1093/hmg/8.1.115

Wheeler, V. C., White, J. K., Gutekunst, C. A., Vrbanac, V., Weaver, M., Li, X. J., Li, S. H., Yi, H., Vonsattel, J. P., Gusella, J. F., Hersch, S., Auerbach, W., Joyner, A. L., & MacDonald, M. E. (2000). Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in Hdh(Q92) and Hdh(Q111) knock-in mice. Human Molecular Genetics, 9(4), 503–513. https://doi.org/10.1093/hmg/9.4.503

Wolf, R. C., Sambataro, F., Vasic, N., Schönfeldt-Lecuona, C., Ecker, D., & Landwehrmeyer, B. (2008). Aberrant connectivity of lateral prefrontal networks in presymptomatic Huntington's disease. Experimental Neurology, 213(1), 137–144. https://doi.org/10.1016/J.EXPNEUROL.2008.05.017

Wood, N. I., & Morton, A. J. (2015). Social Behaviour is Impaired in the R6/2 Mouse Model of Huntington's Disease. Journal of Huntington's Disease, 4(1), 61–73. https://doi.org/10.3233/JHD-140132

Wu, H. P. P., Ioffe, J. C., Iverson, M. M., Boon, J. M., & Dyck, R. H. (2013). Novel, whisker-dependent texture discrimination task for mice. Behavioural Brain Research, 237(1), 238–242. https://doi.org/10.1016/J.BBR.2012.09.044

Wu, L. L. Y., Fan, Y., Li, S., Li, X. J., & Zhou, X. F. (2010). Huntingtin-associated protein-1 interacts with pro-brain-derived neurotrophic factor and mediates its transport and release. Journal of Biological Chemistry, 285(8), 5614–5623. https://doi.org/10.1074/jbc.M109.073197

Wüllner, U., Young, A. B., Penney, J. B., & Beal, M. F. (1994). 3-Nitropropionic Acid Toxicity in the Striatum. Journal of Neurochemistry, 63(5), 1772–1781. https://doi.org/10.1046/j.1471-4159.1994.63051772.x

Wyttenbach, A., Swartz, J., Kita, H., Thykjaer, T., Carmichael, J., Bradley, J., Brown, R., Maxwell, M., Schapira, A., Orntoft, T. F., Kato, K., & Rubinsztein, D. C. (2001). Polyglutamine expansions

cause decreased CRE-mediated transcription and early gene expression changes prior to cell death in an inducible cell model of Huntington's disease. Human Molecular Genetics, 10(17), 1829–1845. https://doi.org/10.1093/HMG/10.17.1829

Xiao, L., Merullo, D. P., Koch, T. M. I., Cao, M., Co, M., Kulkarni, A., Konopka, G., & Roberts, T. F. (2021). Expression of FoxP2 in the basal ganglia regulates vocal motor sequences in the adult songbird. Nature Communications 2021 12:1, 12(1), 1–18. https://doi.org/10.1038/s41467-021-22918-2

Yanagisawa, N. (2018). Functions and dysfunctions of the basal ganglia in humans. Proceedings of the Japan Academy. Series B, Physical and Biological Sciences, 94(7), 275. https://doi.org/10.2183/PJAB.94.019

Yildirim, F., Ng, C. W., Kappes, V., Ehrenberger, T., Rigby, S. K., Stivanello, V., Gipson, T. A., Soltis, A. R., Vanhoutte, P., Caboche, J., Housman, D. E., & Fraenkel, E. (2019). Early epigenomic and transcriptional changes reveal Elk-1 transcription factor as a therapeutic target in Huntington's disease. Proceedings of the National Academy of Sciences, 116(49), 24840–24851. https://doi.org/10.1073/PNAS.1908113116

Yu, Z. X., Li, S. H., Nguyen, H. P., & Li, X. J. (2002). Huntingtin inclusions do not deplete polyglutamine-containing transcription factors in HD mice. Human Molecular Genetics, 11(8), 905–914. https://doi.org/10.1093/hmg/11.8.905

Zamponi, G. W. (2003). Regulation of Presynaptic Calcium Channels by Synaptic Proteins. Journal of Pharmacological Sciences, 92(2), 79–83. https://doi.org/10.1254/JPHS.92.79

Zeitlin, S., Liu, J. P., Chapman, D. L., Papaioannou, V. E., & Efstratiadis, A. (1995). Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. Nature Genetics, 11(2), 155–163. https://doi.org/10.1038/ng1095-155

Zeron, M. M., Hansson, O., Chen, N., Wellington, C. L., Leavitt, B. R., Brundin, P., Hayden, M. R., & Raymond, L. A. (2002). Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington's disease. Neuron, 33(6), 849–860. https://doi.org/10.1016/S0896-6273(02)00615-3

Zhang, J., Peng, Q., Li, Q., Jahanshad, N., Hou, Z., Jiang, M., Masuda, N., Langbehn, D. R., Miller, M. I., Mori, S., Ross, C. A., & Duan, W. (2010). Longitudinal Characterization of Brain Atrophy of a Huntington Disease Mouse Model by Automated Morphological Analyses of Magnetic Resonance Images. NeuroImage, 49(3), 2340. https://doi.org/10.1016/J.NEUROIMAGE.2009.10.027

Zhang, Y., Leavitt, B. R., van Raamsdonk, J. M., Dragatsis, I., Goldowitz, D., MacDonald, M. E., Hayden, M. R., & Friedlander, R. M. (2006). Huntingtin inhibits caspase-3 activation. EMBO Journal, 25(24), 5896–5906. https://doi.org/10.1038/sj.emboj.7601445

Zhang, Y., Xia, M., Jin, K., Wang, S., Wei, H., Fan, C., Wu, Y., Li, X., Li, X., Li, G., Zeng, Z., & Xiong, W. (2018). Function of the c-Met receptor tyrosine kinase in carcinogenesis and associated therapeutic opportunities. Molecular Cancer 2018 17:1, 17(1), 1–14. https://doi.org/10.1186/S12943-018-0796-Y

Zuccato, C., Ciammola, A., Rigamonti, D., Leavitt, B. R., Goffredo, D., Conti, L., MacDonald, M. E., Friedlander, R. M., Silani, V., Hayden, M. R., Timmusk, T., Sipione, S., & Cattaneo, E. (2001). Loss of Huntingtin-Mediated BDNF Gene Transcription in Huntington's Disease. Science, 293(5529), 493–498. https://doi.org/10.1126/SCIENCE.1059581

Zuccato, C., Tartari, M., Crotti, A., Goffredo, D., Valenza, M., Conti, L., Cataudella, T., Leavitt, B. R., Hayden, M. R., Timmusk, T., Rigamonti, D., & Cattaneo, E. (2003). Huntingtin interacts

with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. Nature Genetics, 35(1), 76–83. https://doi.org/10.1038/ng1219

Zuccato, C., Belyaev, N., Conforti, P., Ooi, L., Tartari, M., Papadimou, E., MacDonald, M., Fossale, E., Zeitlin, S., Buckley, N., & Cattaneo, E. (2007). Widespread Disruption of Repressor Element-1 Silencing Transcription Factor/Neuron-Restrictive Silencer Factor Occupancy at Its Target Genes in Huntington's Disease. Journal of Neuroscience, 27(26), 6972–6983. https://doi.org/10.1523/JNEUROSCI.4278-06.2007

Zuccato, C., Marullo, M., Conforti, P., MacDonald, M. E., Tartari, M., & Cattaneo, E. (2008). Systematic assessment of BDNF and its receptor levels in human cortices affected by Huntington's disease. Brain Pathology, 18(2), 225–238. https://doi.org/10.1111/J.1750-3639.2007.00111.X

Zuccato, C.,Valenza, M., & Cattaneo, E. (2010). Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiological Reviews, 90(3), 905–981. https://doi.org/10.1152/PHYSREV.00041.2009

Zweier, C., de Jong, E. K., Zweier, M., Orrico, A., Ousager, L. B., Collins, A. L., Bijlsma, E. K., Oortveld, M. A. W., Ekici, A. B., Reis, A., Schenck, A., & Rauch, A. (2009). CNTNAP2 and NRXN1 Are Mutated in Autosomal-Recessive Pitt-Hopkins-like Mental Retardation and Determine the Level of a Common Synaptic Protein in Drosophila. The American Journal of Human Genetics, 85(5), 655–666. https://doi.org/10.1016/J.AJHG.2009.10.004

ANNEX

Publications derived from this thesis

Rodríguez-Urgellés E., del Toro D, del Castillo Ignacio, Alberch J* and Giralt A*. Striatum-enriched transcription factor Foxp2 ameliorates early psychiatric-like disturbances and molecular alterations in Huntington´s disease. Manuscript under preparation. **Equally contributed to this work*.

Rodríguez-Urgellés E., Casas-Torremocha D, Tornero D, del Castillo Ignacio, Chen W, Parma M, Bortolozzi A, Sánchez-Vives M, Giralt A* and Alberch J*. Thalamic Foxp2 overexpression restores sensoriomotor phenotypes and synaptic deficits in Huntington´s disease. Manuscript under preparation. **Equally contributed to this work*.