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White matter brain connectivity associated with language acquisition: insights from patient studies

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Abstract

Language is acquired practically from birth and continues to expand throughout the entire lifespan. This incredible potential also entails a huge complexity. Although the study of the neural basis of language acquisition has been mainly focused on the brain regions related to language acquisition, the different white matter tracts involved in this process (and connecting most of those regions) and their specific role are still largely unknown. The main goal of the present work was to identify the relevant white matter tracts specifically related to language acquisition. Hence, this thesis includes four studies that evaluated the structural bases of language acquisition through four different impairments affecting this skill, namely Autism Spectrum Disorder (ASD), Huntington's Disease (HD), Primary Progressive Aphasia (PPA), and Post-Stroke Aphasia (PSA). This approach also allowed the assessment of the specific structural differences in each impairment when compared to neurotypical controls.

Study 1 focused on white matter tracts related to impairments in early first language acquisition. To that end, the structural characteristics of the main white matter tracts from 9 non-verbal ASD (nvASD) young participants were compared to those of age-matched groups of individuals with verbal ASD (vASD) and typical development (TD). The main result was the presence of lower fractional anisotropy values in the inferior fronto-occipital fasciculus (IFOF) of nvASD compared to TD participants. This result points to the relevance of the integrity of the ventral tracts (and the IFOF, more specifically) not only for language understanding, but also during its initial acquisition.

Study 2 aimed to explore the integrity of contextual new word learning in individuals with HD. It also aimed to adapt a well-known contextual learning task (CTXL) for its administration in Study 3. The results showed that individuals with HD had more difficulties in contextual word learning than healthy controls. This semantic word learning impairment could be related to the characteristic striatal degeneration present in HD. Moreover, these results helped refining the CTXL task in views of its application in Study 3.

Study 3 tested the performance of 20 individuals with PPA (11 non-fluent and 9 logopenic variant PPA participants) and 23 neurotypical controls on the CTXL task, and then explored the association between the main white-matter language tracts' microstructural properties and the CTXL scores obtained. The results revealed an overall impairment in language acquisition abilities in individuals with PPA when compared to controls. Furthermore, some differences were present between PPA variant groups, as the learning performance was higher in the non-fluent

than in the logopenic group. In addition, learning accuracy was associated with radial diffusivity values in both dorsal and ventral language tracts. These results point to the involvement of both dorsal and ventral tracts in CTXL processes, albeit possibly with different specific sub-functions.

Study 4 examined the language-related white matter tracts supporting verbal short-term memory (vSTM) –a fundamental ability for language acquisition and language rehabilitation– in 19 PSA individuals. The main results revealed statistically significant correlations between the volume of the right uncinate fasciculus (UF) and vSTM scores. These results point to the right UF as a potentially relevant tract for vSTM, at least in PSA.

The results from the present work indicate that the integrity of language acquisition in people with language impairments is associated with the structural properties of several white matter language tracts belonging to both the dorsal and the ventral streams. The specific pathways that were associated with language acquisition were the anterior and long segment of the arcuate fasciculus (AF), the IFOF, and the UF, even if they were possibly engaged in different sub-processes of this function. Additionally, the results show an association of the UF with vSTM functions and a possible involvement of the corticostriatal tracts in semantic integration functions. This investigation also showed the involvement of a wide cerebral network related to the language acquisition process, in line with the results from past research focused on language processing. These four studies advance our knowledge regarding the structural neural basis of language acquisition and the specific role of different white matter pathways within this process. The overall findings of this work not only provide new theoretical insights but could also have a clinical impact at different levels.

Resum

El llenguatge s'adquireix pràcticament des del naixement i continua creixent al llarg de tota la vida. Aquest increïble potencial també comporta una gran complexitat. L'estudi dels substrats cerebrals de l'adquisició del llenguatge s'ha centrat principalment en la investigació de les regions cerebrals relacionades amb aquest procés, mentre que les diferents vies de substància blanca involucrades en aquest procés i els seus rols específics són encara desconeguts. L'objectiu principal d'aquesta dissertació va ser identificar els tractes de substància blanca relacionats amb l'adquisició del llenguatge. Aquesta tesi inclou quatre estudis en els quals es van avaluar les bases estructurals de l'adquisició del llenguatge en quatre trastorns diferents, com són el trastorn de l'espectre autista (ASD), la malaltia de Huntington (HD), l'afàsia progressiva primària (PPA) i l'afàsia post-ictus (PSA). Aquest plantejament també va permetre examinar les diferències estructurals específiques de cada trastorn en comparació amb els controls neurotípics.

L'estudi 1 es va centrar en la investigació d'alteracions relacionades amb deficiències en l'adquisició de la llengua materna. Amb aquesta finalitat, es van comparar les característiques estructurals de les principals vies de substància blanca de 9 participants amb autisme no verbal (nvASD) amb les de grups aparellats d'individus amb autisme verbal (vASD) i amb un desenvolupament típic (TD). El principal resultat va ser una disminució dels valors de *fractional anisotropy* ('anisotropia fraccional') del fascicle fronto-occipital inferior (IFOF) en nvASD en comparació amb els participants amb TD. Aquest resultat apunta a la importància de la integritat de les vies ventrals (i més concretament de l'IFOF) no només per a la comprensió del llenguatge, sinó també per a la seva correcta adquisició inicial.

L'estudi 2 va tenir com a objectiu explorar la integritat de l'aprenentatge contextual (CTXL) de noves paraules en persones amb HD. També pretenia millorar l'adaptació d'una tasca pre-existent de CTXL per a la seva administració a l'estudi 3. Els resultats van mostrar que els individus amb HD tenien més dificultats per a realitzar la tasca de CTXL que els controls sans. Aquestes diferències podrien estar relacionades amb la degeneració estriatal característica de l'HD. L'estudi també va ajudar a refinar la tasca de CTXL de cara a la seva aplicació en l'estudi 3.

A l'estudi 3 es van investigar les vies de substància blanca que donen suport al CTXL mitjançant l'avaluació de 20 individus amb PPA (11 de la variant no fluent i 9 de la variant logopènica) i 23 controls neurotípics durant la tasca de CTXL, i l'exploració de l'associació entre les propietats microestructurals del tractes de llenguatge i les puntuacions de CTXL obtingudes. Els resultats van revelar un deteriorament general de la capacitat d'adquisició lingüística dels individus amb PPA en comparació amb els controls. A més, es van observar diferències entre els grups de PPA,

ja que la capacitat d'aprenentatge era més elevada en individus de la variant no fluent que en la logopènica. Altrament, aquesta capacitat d'aprenentatge es va associar amb els valors de radial diffusivity ('difusivitat radial') tant de vies lingüístiques dorsals com ventrals. Aquests resultats apunten a la implicació tant dels tractes dorsals com ventrals en el procés de CTXL, encara que possiblement amb sub-funcions específiques diferents.

L'estudi 4 va examinar els feixos de substància blanca relacionats amb llenguatge que donen suport a la memòria verbal a curt termini (vSTM), una capacitat fonamental per a l'adquisició i rehabilitació del llenguatge, en 19 persones amb PSA. Els resultats principals van revelar correlacions estadísticament significatives entre el volum del fascicle uncinat dret (UF) i les puntuacions de vSTM. Aquests resultats assenyalen l'UF dret com a tracte rellevant en funcions de vSTM, com a mínim en PSA.

El resultats d'aquest treball indiquen que la integritat de l'adquisició lingüística en individus amb trastorns del llenguatge està relacionada amb les propietats estructurals de diversos feixos de substància blanca que pertanyen tant a la via lingüística dorsal com a la ventral. Els feixos específics associats amb l'adquisició del llenguatge han estat el segment anterior i directe del fascicle arquejat (FA), l'IFOF i l'UF, tot i que possiblement estaven involucrats en diferents sub-processos de l'aprenentatge lingüístic. A més, els resultats mostren una associació de l'UF amb funcions de vSTM, així com una possible implicació dels tractes cortico-estriatals en funcions d'integració semàntica. Aquest treball també ha confirmat que el procés d'adquisició del llenguatge depèn d'una àmplia xarxa cerebral, tal i com ja han indicat els resultats d'estudis anteriors centrats en les bases del processament lingüístic.
Aquests quatre estudis permeten augmentar el nostre coneixement sobre les bases estructurals de l'adquisició del llenguatge i sobre el paper específic de diferents feixos de substància blanca en aquest procés. Les troballes d'aquesta dissertació no només proporcionen avenços teòrics sinó que també podrien tenir un impacte clínic a diferents nivells.

List of frequently used abbreviations

AF: Arcuate Fasciculus

CTXL: Contextual word Learning

DTI: Diffusion Tensor Imaging

FA: Fractional Anisotropy

HD: Huntington's Disease

IFOF: Inferior Fronto Occipital Fasciculus

ILF: Inferior Longitudinal Fasciculus

LA: Language Acquisition

ASD: Autism Spectrum Disorder

- **nvASD**: non-verbal ASD
- **vASD**: verbal ASD

PLI: People with Language Impairments

PPA: Primary Progressive Aphasia

- **nfvPPA**: non-fluent variant PPA
- **lvPPA**: logopenic variant PPA

PSA: Post-Stroke Aphasia

RD: Radial Diffusivity

UF: Uncinate Fasciculus

vSTM: verbal Short-Term Memory

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Chapter 1 - Introduction

1. Introduction

1.1 The importance of language

Language is a unique and extraordinary human ability (J. P. Rauschecker & Scott, 2009) largely responsible of how we are and how we live. Thanks to language, humans are able to communicate and transmit a wide array of concepts: from feelings to complex ideas; from past events to future plans; from real experiences to imaginary situations. Language has enabled our species to organize thoughts and build ideas upon them. Humans can simulate the future through language, but also become aware of past experiences from other individuals so we can learn things without having to face them. Importantly, it made possible the transmission of knowledge from generation to generation, and beyond. Given that we can write down language –as I am doing right now– we do not depend on spoken language to pass on ideas, getting rid of temporal and spatial constraints and enabling fast incremental learning for upcoming generations. This represents an enormous evolutionary advantage (Suddendorf, Addis, & Corballis, 2009). Hence, the potential of human language goes hand in hand with an incredible complexity. Any language is comprised by a vast lexicon, with each word being associated with specific phonological and semantic information. In turn, words are usually organized into sentences, which are governed by grammar and syntax rules that determine how messages are interpreted in meaningful ways. Additionally, other aspects such as prosody, context, or cultural aspects can influence the ultimate interpretation of the message.

The linguistic learning capacity of humans is practically unlimited, as our mother tongue vocabulary keeps growing over lifespan. This learning ability enables humans to cope with the constant evolution of language in its different forms (the transformation of meanings, appearance of neologisms, etc). On top of that, at least half of the world's population speaks more than one language (Grosjean, 1982), despite the considerable existing differences between languages. Moreover, this language acquisition is, in most cases, unconscious and effortless. That might be the reason why we take it for granted: it is not until we lose it that we realize how much we use it and need it on our everyday lives, or how easy it is to lose it and how effortful it is to get it back (Dronkers, Ivanova, & Baldo, 2017). The loss of language skills (i.e., aphasia) can be a big problem for both the person who suffers it and the people around them. The repercussions of language impairments go far beyond the communication problems, as they have impact on the patient's work and social activities (Spaccavento et al., 2013). Several studies show that people with aphasia report high levels of depression (Kauhanen et al., 2000) and social exclusion (Parr, 2007), together with low levels of quality of life (Hilari, Wiggins, Roy, Byng, & Smith, 2003; Ross & Wertz, 2003). Therefore, clinical research is imperative in order to search for ways to mitigate these difficulties.

However, that is not the only reason for conducting studies with these individuals. The investigation of language skills in People with Language Impairments (PLI)* has great relevance at different levels. Given the focus of this thesis, I will provide an explanation for the importance of the studies with PLI in the next section, framing it in relation to the study of Language Acquisition (LA) in the presence of language impairments, although many of these points could be valid for other language related aspects or even for other domains.

1.2 The relevance of patient studies in language acquisition

On the one hand, investigating language acquisition (LA) in PLI can increase our knowledge about the basis of LA in the healthy brain. Since the early days of cognitive neuroscience, studies with PLI have been one of the main sources of knowledge (Mirman, Chen, et al., 2015). Examples of this are the seminal studies by Broca (1861), Wernicke (1874), or Lichtheim (1885) that laid the foundations for current linguistic processing models. In the same way, subsequent studies focusing on aphasia research have allowed us to refine the theories from those initial studies and to build on our current knowledge on the bases of language processing and acquisition. Some of these studies have made it possible to establish lesion-behavior associations revealing, for example, that lesions compatible with Broca's aphasia typically involve other regions than just Broca's area, including IFG, MFG and/or basal ganglia (N.F. Dronkers, Redfern, & Knight, 2000) and that individuals without apraxia of speech tend to have lesions sparing the pre-central gyrus (Basilakos, Rorden, Bonilha, Moser, & Fridriksson, 2015; Itabashi et al., 2016). In short, studies with PLI have confirmed that aphasic syndromes are not ascribable to lesions in small discrete regions such as Broca's or Wernicke's areas, but rather to alterations in a more extensive and complex network (Dronkers et al., 2017). Likewise, there have also been theoretical advances on the bases and mechanisms of LA thanks to studies with patients (see Peñaloza, Martin, Laine, & Rodríguez-Fornells, 2022 for a review). These studies have shown that individuals with aphasia, despite having language processing impairments, are capable of learning new words through explicit (Coran, Rodriguez-Fornells, Ramos-Escobar, Laine, & Martin, 2020b; L. Tuomiranta et al., 2011), implicit (Peñaloza et al., 2015, 2017; Schuchard & Thompson, 2017), and incidental learning (Breitenstein, Kamping, Jansen, Schomacher, & Knecht, 2004; Peñaloza et al., 2016) although this learning is usually lower and/or slower than that of healthy controls (Breitenstein et al., 2004; Peñaloza et al., 2015, 2017, 2016; L. Tuomiranta et al., 2011).

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*It is important to highlight that the majority of studies carried out with patients that tried to investigate the bases of some linguistic process focused on the study of aphasia. The definition of the term aphasia is not a trivial matter, as can be seen from its various attempts over the years, with varying success (McNeil & Pratt, 2001). Brenson (1979) defined it as "the loss or impairment of language caused by brain damage". More recent studies offer an alternative definition, such as "the disturbance of any or all the skill, associations and habits of spoken language, produced by injury to certain brain areas that are specialized for these functions" (Goodglass & Kaplan, 1983). In any case, these definitions do not include cases like individuals that don't acquire language in the first place, language problems not related to brain damage or language problems secondary to alterations in non-language related brain areas. The general idea behind this thesis is that a process as complex as language acquisition can be approached from different perspectives and by studying different disorders -not just aphasia-, which can provide different type of information. That is why in this introduction I used People with Language Impairments (PLI), a term that seeks to be broader and more inclusive.

Additionally, some studies have uncovered the importance of learning modality in LA. An illustrative example is the study by Tuomiranta and colleagues (2014), showing a single case of an aphasic patient who presented impaired word learning in the auditory modality -due to impaired phonology- but spared orthographic learning. Other studies have focused on the identification of predictors of LA success. One of the potential predictors identified appears to be aphasia severity, which has been associated with word learning ability, as well as with anomia therapy response (Dignam et al., 2016; Marshall, Freed, & Karow, 2001). Findings also suggest that lesion location plays a role in learning, as larger LA impairments have been associated with frontal lesions in individuals with aphasia (Peñaloza et al., 2015, 2016). Similarly, working memory appears to be crucial for LA, as shown by studies that have related the integrity of this ability with LA success (Freedman & Martin, 2001; Peñaloza et al., 2015, 2017, 2016; Tuomiranta, Rautakoski, Rinne, Martin, & Laine, 2012). These are just some examples that demonstrate the theoretical advances that have recently been made related to LA by the investigation of PLI. These studies use the advantage provided by focal lesions associated with specific impairments, which can be highly informative about the role that the affected brain region or connection has with respect to a given process (Mirman, Zhang, Wang, Coslett, & Schwartz, 2015). Therefore, the study of LA in PLI can help determine which structures are crucial for the integrity and correct development of LA process in the healthy brain. It can help understand the level of interplay of subprocesses related to LA such as language perception or memory systems, and its neural underpinnings (Peñaloza et al., 2022). But the theoretical advances obtained by this approach are not only transferable to the healthy brain. Studies with PLI can inform about processes that occur in the presence of impairment as well, regardless of whether these mechanisms are in place in the healthy brain or not. Some examples of these processes are brain plasticity and/or reorganization, structural or functional redundancy, diaschisis or compensation, among others (Kelly & Armstrong, 2009; Van Hees et al., 2014; see Fornito, Zalesky, & Breakspear, 2015 for a review). Additionally, these studies can also contribute to improving therapy models following brain damage, given that proven effectiveness of certain therapeutical approaches contrasts with the lack of knowledge regarding their underlying mechanisms (Brady, Kelly, Godwin, Enderby, & Campbell, 2016; Dignam et al., 2016).

On the other hand, the study of LA ability in PLI not only entails potential theoretical advances but can also have an important clinical impact. First, characterizing the integrity of LA can help improving patient classification. In some language disorders, such as Post-Stroke Aphasia (PSA) or Primary Progressive Aphasia (PPA), patients are classified into different variants or subtypes depending on the integrity of their linguistic and non-linguistic abilities (Goodglass, Kaplan, & Barresi, 2001; M. L. Gorno-Tempini et al., 2011). However, this classification is often complicated, given that there is great feature variability within each variant. In addition, some

patients present characteristics that do not fit completely in any variant (Ingram et al., 2020). The integrity of LA ability has not been considered as a defining factor when establishing these classifications (Basso, 2003; Caramazza & Hillis, 1993). Therefore, a characterization of the integrity of LA ability could uncover differences between variants or subgroups, which could in turn contribute to the improvement of the classification process and the subsequent patients' management.

Secondly, characterizing the integrity of LA ability in PLI can lead to an improvement in their treatment. LA has been proposed to have a central role in recovery following language therapy (Coran et al., 2020b). For instance, anomia therapy aims to reinforce the association between words and meanings, and to regain access to lexical elements that were previously known (Basso, Marangolo, Piras, & Galluzzi, 2001; Nickels, 2002). These processes share mechanisms with LA and have even been equated to it (Helm-Estabrooks, 2002). If these mechanisms are understood and examined in PLI, they can be used to adapt the treatment to each patient, improving its efficacy. The ultimate goal of any language treatment should be to tailor it to each patient taking into account their deficits and preserved abilities, as well as their individual learning style and preferences (Peñaloza et al., 2022). In any case, potential therapy improvements must be seen as a sub-product of the theoretical gains of PLI studies discussed above. In order to properly adapt and improve therapeutic approaches to the patients, clinicians must first have a reliable model of language rehabilitation that includes: i) a theoretical account of the mechanisms present during LA; ii) information regarding the neural basis underlying said mechanisms; iii) an accurate evaluation of the mechanisms and brain structures affected in each patient; iv) knowledge about which of these mechanisms are amenable to improvement, and which are not; and v) a strategy on how to improve the functions that are eligible for improvement, with a special focus on which tasks can be used and how (L. Tuomiranta, Laine, Rautakoski, Kiran, & Nickels, 2015). Although our research field is far from this comprehensive understanding, studies on LA with patients can provide relevant clues in this regard.

Finally, some studies have argued that the integrity of learning abilities can help predict the success of anomia therapies (Dignam et al., 2016; Tuomiranta et al., 2014). Anomia is one of the most prevalent symptoms in PLI, meaning its therapy is crucial and takes place in most cases of language impairment (Maher & Raymer, 2004). Therefore, the evaluation of naming and word learning abilities in PLI could eventually help determine patients' prognosis, allowing for the evaluation of improvement potential in each case before the start of the therapy (Peñaloza et al., 2022).

In short, the information that can be obtained from the study of LA abilities in PLI is numerous and varied, with a potential relevance at both the theoretical and clinical levels. Consequently, there has been a growing interest in the field of cognitive neuroscience regarding the bases of

language processing and acquisition in PLI. This has greatly contributed to achieving the level of knowledge we currently have about these processes. The following section is devoted precisely to reviewing the state of the art regarding the current neurocognitive models of language processing and LA described in the literature, as well as the mechanisms and neural basis associated with these processes.

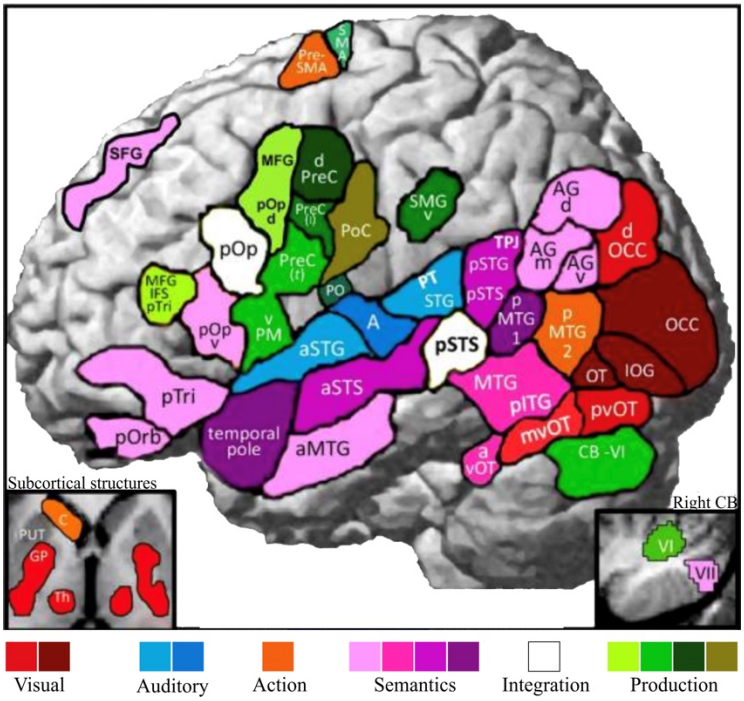

Figure 1. Location of brain activations related to language functions (adapted from Price, 2012). Summary of language related brain activations. The colors indicate the type of task or stimuli that triggered the activations: red = visual stimuli; blue = auditory stimuli; pink/purple = semantics; white = integration, both production and perception tasks; green = production tasks.

1.3 The neural correlates of language

1.3.1 Cortical anatomy of language processing

Our understanding of how the brain processes linguistic information has grown considerably since the first and pioneering works of Broca and Wernicke (Broca, 1861; Wernicke, 1874). The modern view of the functional anatomy of language processing is much more complicated given that the studies using functional techniques (C. J. Price, 2012) and cortical stimulation mapping (Ojemann, 1991; Rofes et al., 2019) have allowed to identify a significant number of brain regions involved in this process beyond Broca's and Wernicke's areas (see Figure 1). The influential model proposed by Hickok and Poeppel a couple of decades ago (Hickok & Poeppel, 2000, 2004, 2007) has helped in making sense of this collection of regions that are involved in language and speech processing. According to this model, language might be processed by two differentiated

streams, which project into both sides of the lateral fissure (see Figure 2). On the one hand, the dorsal stream would be a left-lateralized network in charge of the sensory-motor integration for speech-related motor control (i.e., sound-to-motor mapping) (Hickok & Poeppel, 2007; J. P. Rauschecker & Scott, 2009). Anatomically, this stream principally involves anterior frontal regions, including the inferior frontal gyrus (IFG) and premotor cortex (PMC), the parieto-temporal boundary, and the inferior parietal lobe (IPL) (Hickok & Poeppel, 2007). On the other hand, the ventral stream would be related to language comprehension or, in other words, the sound-to-meaning mapping. As for its cortical representations, this stream might be more bilaterally organized and cover most part of the temporal lobe, namely the posterior parts of the superior (STG), middle (MTG) and inferior temporal gyri (ITG) and the anterior temporal lobe (ATL), as well as inferior frontal regions (Hickok & Poeppel, 2007). This model places the emphasis on the cortical anatomy of speech processing, overlooking the importance of some extra-sylvian regions that have been shown to be active during language processing tasks, such as the cerebellum (Mariën & Borgatti, 2018; Pliatsikas, Johnstone, & Marinis, 2014). Another example of such regions is the basal ganglia, suggested to participate in syntactic processing (Friederici & Kotz, 2003) and overt speech production (Koelsch et al., 2009), and whose lesion has been described to induce aphasia (Lieberman, 2016).

Despite this model potentially not being able to integrate all the regions that have been described as related to language processing, it is a relevant account that successfully explains the cortical basis of this complex process and is backed by a large body of evidence(Almairac, Herbet, Moritz-Gasser, de Champfleur, & Duffau, 2015; Hickok & Poeppel, 2007; Nasios, Dardiotis, & Messinis, 2019; J. P. Rauschecker & Scott, 2009; Rodriguez-Fornells, Cunillera, Mestres-Missé, & De Diego-Balaguer, 2009). Overall, the cortical anatomy of language processing and its organization in streams, with the already discussed dorsal-ventral split, are well-defined and consistently supported in the field.

However, the human brain not only needs to handle the computations necessary for the comprehension and production of language, but also needs to initially acquire the components of the language itself. Therefore, an unresolved question remains: how are we able to acquire all this linguistic knowledge in the first place? It is difficult to define how we process language without understanding first how we acquire and integrate it into our systems. Therefore, existing language processing models should be complemented by studies aimed at uncovering the neural bases and dynamics regarding the incorporation of new linguistic information.

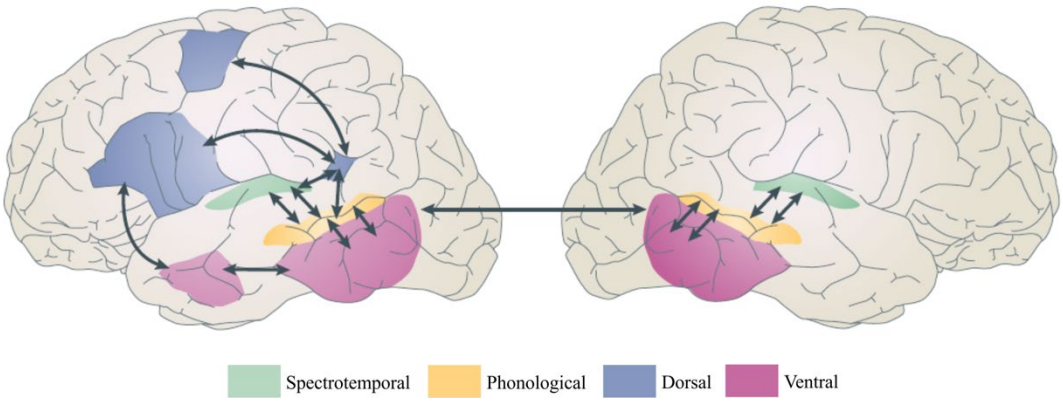

Figure 2. Depiction of the dual language stream model of language processing (adapted from Hickok & Poeppel, 2007). The colors indicate different proposed functions for the cortical areas and the arrows indicate the direction of the information flow. Green areas are supposedly involved in the first step of speech processing which is the spectrotemporal analysis of the speech signal. After that, phonological processing is carried out at the superior temporal sulcus, painted in yellow. From there, two different streams process the auditory information in parallel: the dorsal stream areas (in blue) map the sensory and phonological representations onto articulatory-based representations while the ventral stream (in pink) map sensory and phonological representation onto lexical-semantic representations.

1.3.2 Cortical and subcortical anatomy of language acquisition

1.3.2.1 Vocabulary Learning Mechanisms

Language acquisition (LA) is a highly complex and multifaceted process, being vocabulary acquisition one of its primary aspects (Bloom, 2000). In vocabulary acquisition, a learner is exposed to one or more unknown linguistic elements –whether in form, meaning, or both– that they must decipher and retain. This learning capacity could be supported by various mechanisms, such as statistical learning or associative learning.

Statistical learning (SL) is a mechanism that enables to capture the regularities present in the environmental stimuli and to extract their patterns (Romberg & Saffran, 2010; Siegelman & Frost, 2015). It is considered a general mechanism as it has been described for new information acquisition in different domains such as the auditory (e.g., Saffran, Johnson, Aslin, & Newport, 1999), visual (e.g., Fiser & Aslin, 2001), or tactile systems (e.g., Conway & Christiansen, 2005). This learning mechanism has also been associated with LA and, more specifically, with one of the first aspects of vocabulary acquisition: speech segmentation (J. R. Saffran, Aslin, & Newport, 1996). In a linguistic context, an individual is rarely exposed to isolated words with clear boundaries between them but rather to a continuous speech stream. Therefore, before learning the meaning of words, one must learn to divide this speech stream into individual chunks. It has been suggested that SL is a key mechanism in speech segmentation as it allows to calculate transitional probabilities between syllables, which vary within and between words (J. R. Saffran, Aslin, et al., 1996; J. R. Saffran, Newport, & Aslin, 1996). This ability is present from shortly after birth (Teinonen, Fellman, Näätänen, Alku, & Huotilainen, 2009) until adulthood (Cunillera et al., 2009;

López-Barroso et al., 2015) and has been described to be supported by the STG (Cunillera et al., 2009; Karuza et al., 2013) and the IFG (Karuza et al., 2013). Furthermore, it has been observed to be sensitive to age and left-hemisphere injury (Fama, Schuler, Newport, & Turkeltaub, 2022), and that its integrity relates to hippocampal volume and integrity (Schevenels et al., 2022). Interestingly, reports show that it can remain functional even after left-hemisphere injury, as observed in a sample of people with chronic Post-Stroke Aphasia (PSA; Peñaloza et al., 2015). Once the words have been segmented, the learner must be able to assign them a meaning, or in other words, to perform word-to-world mapping. This process can be complicated at times because a word can be associated with multiple referents in a single given learning context. However, this uncertainty can be resolved in subsequent encounters with that word in a process known as Cross-Situational Learning (CSL; Yu & Smith, 2007). Although this type of learning is different from that of speech segmentation, CSL also appears to be related to SL mechanisms as it assists the learner in the disambiguation process by computing co-occurrences between a word and potential referents across exposures (Yu & Smith, 2007). As it happens in speech segmentation, CSL seems to be present across the lifespan (L. Smith & Yu, 2008; Yu & Smith, 2007) and is also present, although reduced, in PSA (Peñaloza et al., 2017).

Therefore, if true, CSL should allow to disambiguate the referent indeterminacy. At the word-to-world mapping point, LA could unfold by means of associative learning mechanisms (MacWhinney, 1987; Merriman, 1999; Regier, 2005). Associative learning was first described in Pavlov's experiments (1927) and is one of the most fundamental forms of psychological change, allowing human's learning at different life stages (M. H. Kelly & Martin, 1994; Mackintosh, 1965; Shanks, 1995). When applied to word learning, this mechanism would allow learners to associate a concept with its corresponding word form when presented together (McMurray, Horst, & Samuelson, 2012). This mechanism fits the slow and errorful nature of LA observed in its early stages (L. B. Smith, 2000), and even if it may proceed without solving referential ambiguity and without constraints, they seem to facilitate the learning process (McMurray et al., 2012).

However, a series of studies have questioned whether CSL is behind word-to-world mapping and propose that this disambiguation process occurs instead through a propose-but-verify strategy: in the first exposure to a new word, a potential meaning is assigned, which is verified or discarded in subsequent contexts until a definitive association is assigned to the word (Medina, Snedeker, Trueswell, & Gleitman, 2011; Trueswell, Medina, Hafri, & Gleitman, 2013). Accordingly, this word-to-world mapping could be achieved through a process dubbed Fast Mapping (FM). FM appears to be a hippocampal-independent mechanism (Sharon, Moscovitch, & Gilboa, 2011) that allows for the learning of word-referent associations after very few exposures and over a long period of time (Carey & Bartlett, 1978). However, reports can be found in the literature questioning the retention capacity achieved with FM, thus arguing that successful word-reference selection cannot be equated to learning without retention (Horst & Samuelson, 2008). Other

accounts have put into question FM's hippocampal independence (Greve, Cooper, & Henson, 2014) or even the mere existence of this mechanism in relationship to vocabulary acquisition (Cooper, Greve, & Henson, 2019).

In a complementary way, the constraint approach is a theory that assumes that new word learners, especially children, present a series of biases that help them in the resolution of the referential ambiguity inherent to the process of new word learning, by providing them with information not available in the context (Golinkoff, Mervis, & Hirsh-Pasek, 1994; Woodward & Markman, 1998). According to this approach, a learner will tend to assume that a new word will refer to whole objects instead of parts of it, or to basic categories instead of super or subordinate categories. Another relevant bias is the name-nameless category principle: when presented with two objects and two possible labels, if a learner already knows an object-label association, they will automatically assign the new label to the unknown object (Grassmann & Tomasello, 2010; Mervis & Bertrand, 1994). The existence of these biases could guide and facilitate the LA process assuming that new word learning is inferentially based, as proposed by some of the accounts presented above. However, this approach has been challenged on several grounds, as it has failed to explain how the different bias interact or how learners are able to reconcile them with learning object properties, synonyms, or super- and supraordinate labels (McMurray et al., 2012).

The mechanisms presented above do not have to be mutually exclusive but could occur in different situations or on different time scales (McMurray et al., 2012), thus explaining the great linguistic learning capacity presented by humans. Nonetheless, what is clear from the evidence presented above is that the mechanisms involved in language acquisition (or at least in vocabulary acquisition) are not fully understood and new research is needed to disentangle their roles in the recovery of language in PLI.

1.3.2.2 Language Acquisition models

Some studies have proposed models that can explain LA and its neural bases comprehensively. Theoretical frameworks aiming to explain the foundations of LA need to integrate the knowledge of language processing with existing memory models.

One such example is the ***Declarative/Procedural Model*** (Ullman, 2001, 2004), which proposes that LA and its subsequent mastering relies on two separated capacities: lexical knowledge and syntax processing. The first includes the rapid acquisition of all the information concerning word sounds, meanings, and categories, as well as the association between these elements. This component relies on the declarative memory system and, thus, it initially engages the hippocampus and middle temporal lobe (MTL) structures (Ullman, 2001, 2004). However, consolidated lexical knowledge gradually becomes less MTL dependent, relying more on

temporo-parietal cortical areas (Ullman, 2004). On the other hand, the gradual and slow acquisition of language rules including syntax, morphology, and phonology is rooted in frontal, basal-ganglia, and cerebellar structures as it relies on the procedural-memory system (Ullman, 2001). However, whether this division of tasks changes with age or whether these rules apply equally for both native (L1) and second (L2) LA is still a matter of debate (Rodriguez-Fornells et al., 2009; Ullman, 2001).

Another supported theoretical model of LA was proposed by Davis and Gaskell (2009) based on the ***Complementary Learning System*** theory for memory (McClelland, McNaughton, & O'Reilly, 1995). This account suggests that lexical acquisition occurs in two different stages. In the initial stage, a rapid initial acquisition of lexical units would be supported by hippocampal and MTL structures and stored as context-specific episodic memories. In the second stage, a slower process would enable the consolidation of these memory traces into more stable representations, that could then be integrated into the existing declarative long-term memory system. In comparison to the *declarative/procedural model,* this model suggests a gradual reduction in the dependence of memory on the hippocampus in favor of neocortical regions (Davis & Gaskell, 2009), as supported by evidence found in fMRI studies with healthy subjects (Breitenstein et al., 2004; Gore, Woollams, Bruehl, Halai, & Ralph, 2022; Mestres-Missé, Càmara, Rodriguez-Fornells, Rotte, & Münte, 2008).

A more comprehensive view is offered by the ***Integrative Neurophysiological Model*** (INM) of language learning, as it incorporates the evidence related to language processing (Hickok & Poeppel, 2007), learning and consolidation (Nadel & Moscovitch, 1997), and cognitive control processes (Krashen, 1982) to account for the cognitive mechanisms and neural underpinnings engaged during LA (Rodriguez-Fornells et al., 2009, see Figure 3). According to the INS model, a successful LA process requires the recruitment of three main interfaces in a coordinated manner, each being activated to a greater or lesser extent depending on the specific requirements of the learning process (Rodriguez-Fornells et al., 2009). First, the dorsal auditory-motor interface is related to mapping new word forms into articulatory representations and plays a prominent role in the acquisition of new vocabulary. Neuroanatomically, this interface largely coincides with the dorsal language stream defined by Hickok and Poeppel (2007), mainly engaging the left posterior STG, the PMC, and the posterior IFG, in addition to regions of IPL that have been mostly related to verbal working memory functions (Cunillera et al., 2009; Karuza et al., 2013; Rodriguez-Fornells et al., 2009). Secondly, the ventral meaning integration interface is related to word-to-meaning mapping. This network is involved in various processes such as the extraction of relevant semantic information from a word or a linguistic context, the activation of the appropriate semantic features and corresponding lexical candidates, or the semantic selection and disambiguation processes in case of conflict (Mestres-Missé et al., 2008; Ripollés et al., 2017).

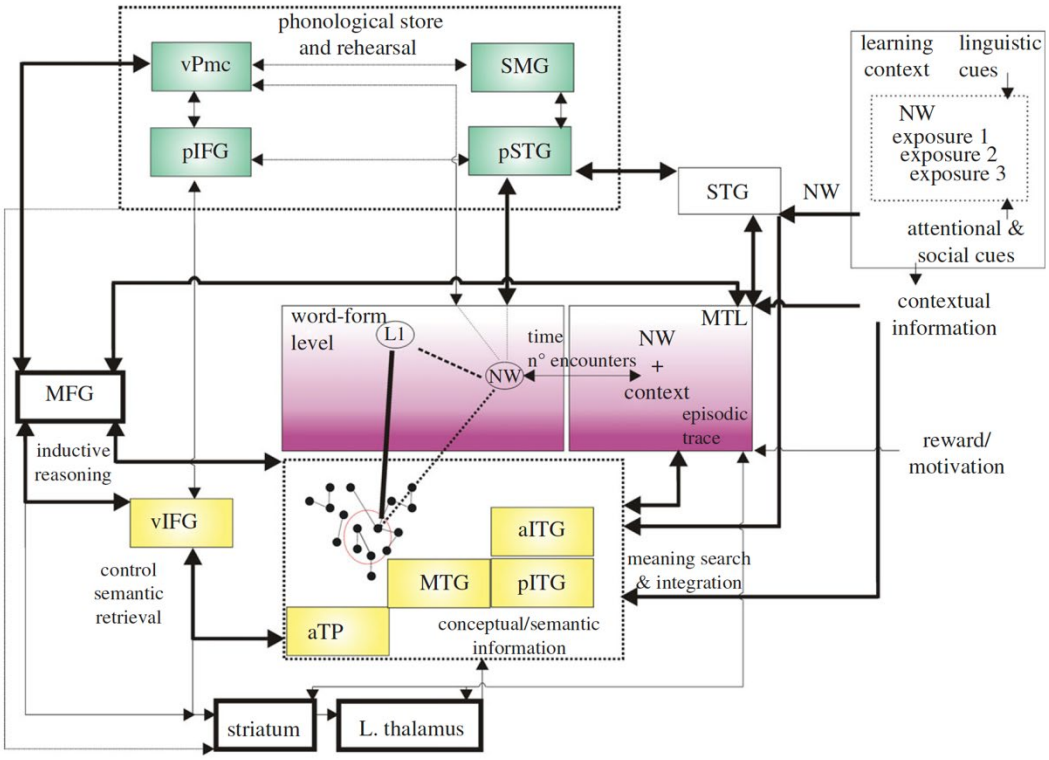

Figure 3. Neural bases of the Integrative Neurophysiological Model of language learning (adapted from Rodriguez-Fornells et al., 2009). The three main streams described in the model are shown in different colors: the dorsal auditory-motor interface in green, the ventral meaning integration interface in yellow and the episodic-lexical interface in purple. New words are first processed by the STG and are then channeled to the dorsal route. On the other hand, new word information and contextual information enter the ventral stream and activate regions involved in the storage and retrieval of semantic information. After repeated exposure, the episodic-lexical interface is triggered to allow the association of words and meanings and the creation of a new lexical representation. Depending on the learning context, the striatum-thalamic loop can be activated for reward and motivational learning and the MFG can participate with inductive reasoning functions. Abbreviations: NW = new word; L1 = lexical trace; MTL = medial temporal lobe; aITG = anterior inferior temporal gyrus; MTG = medial temporal gyrus; aTP = anterior temporal pole; vIFG = ventral inferior frontal gyrus; pIFG = posterior IFG; MFG = middle frontal gyrus; vPMC = ventral premotor cortex; SMG = supramarginal gyrus; pSTG = posterior superior temporal gyrus.

In terms of its neural underpinnings, this second interface is supported by the MTG, the ITG, the ATL and the ventral IFG (Anthony Steven Dick, Bernal, & Tremblay, 2014; Rodriguez-Fornells et al., 2009). Thirdly, the episodic-lexical interface is related to the declarative memory system as described in the complementary learning system model. Accordingly, it has been proposed to recruit MTL regions like the hippocampus and parahippocampus, and to play a crucial role in the initial binding of a novel word form to its conceptual representation, even after very few exposures (Mestres-Missé et al., 2008). The above-described would represent the main interfaces related to LA. However, there are other relevant interfaces or networks that support and regulate this LA process, such as the middle prefrontal cortex in relation to inductive rule-learning (Rodriguez-Fornells et al., 2009). Moreover, the striatal circuits (thalamo-striatal and fronto-striatal networks) appear to have a crucial role in semantic integration and executive control over language processing (De Diego-Balaguer et al., 2008; Stanc et al., 2020). Finally, this model

suggests that all these interfaces can be modulated by other regions that control higher-level cognitive functions such as the prefrontal cortex.

The above-described models try to explain the neural correlates of LA from different perspectives. Despite their apparent differences, they agree on different aspects like the engagement of cortical areas in the early stages of LA, or the fact that the acquired linguistic information initially depends on MTL structures. Although they do not state it explicitly, another aspect of convergence between the models is the assumption that the learner must be able to retain and manipulate linguistic information so that it can be encoded and memorized. Therefore, all these models are compatible with the view that Short-Term Memory (STM) and working memory are crucial mechanisms in LA. STM is the capacity to store a determined amount of information for a limited amount of time (N. Cowan, 2008). This ability is thought to be a subcomponent of working memory, as the latter is thought to incorporate processing operations on the stored information (N. Cowan, 2008). According to Baddeley and Hitch (1974), working memory involves two principal components: the phonological loop for verbal storage, and the visuospatial sketchpad related to visuo-spatial representations (see A. Baddeley, 2003 for a review). From these two, the *phonological loop* has been especially related to LA and vocabulary learning (Elisabet Service & Kohonen, 1995) as it may allow the temporal retention of new phonological forms and their subsequent transfer into long-term memory (Baddeley, Gathercole, & Papagno, 1998). The cortical correlates of this phonological loop include the superior temporal cortex, possibly related to word perception, along with parietal, inferior frontal and premotor cortices, which have been associated with subvocal rehearsal, in particular (Buchsbaum & D'Esposito, 2008; Jonides et al., 1998; McGettigan et al., 2011). This influential working memory model –as well as some more recent ones (Gupta, 2003)– focus on the temporal maintenance of the phonological aspects of language. However, more recent work has provided evidence on the existence of separate constituents of verbal STM into phonological and semantic components, which would also present separable neural correlates (Martin, Ding, Hamilton, & Schnur, 2021; but see Martin, 2005 for a previous comprehensive review). According to this view, *phonological verbal STM* would be supported by the supramarginal gyrus (SMG), and supplementary motor and posterior IFG regions, while the *semantic STM* would rely more on the Angular Gyrus (AG) and the posterior superior temporal sulcus (pSTS). In any case, these STM/working memory mechanisms are a key piece in the LA process and complement the neuroanatomical accounts of LA presented above. Therefore, STM ability has been repeatedly associated with new word learning ability in healthy participants (Alan Baddeley et al., 1998; Susan E. Gathercole, 2006), as well as in people with aphasia (M. L. Freedman & Martin, 2001; Peñaloza et al., 2015, 2017). So far, I have discussed the importance of patient studies and how they have allowed us to obtain the current models of language processing and learning, along with their neural underpinnings. However, when explaining these models, I have used words such as stream, pathway or interface.

These concepts already suggest that linguistic processes are not carried out by isolated cortical regions but rather by connected areas. And while the function of the regions is, in general, well known, the functions of the connections between them are far less understood (Shekari & Nozari, 2023). Thus, the following chapter focuses precisely on reviewing what is known about these language-related connections: what they are and how they can be studied, along with their known functions up until today and the processes they have been related to.

1.4 Structural connectivity

The body of evidence obtained in recent years suggests that language, like most cognitive functions, depends on a broad network of brain regions (Dragomir & Omurtag, 2023). Although some lower-level functions, such as speech perception or articulation might be more limited to certain brain regions, most language-related processes are widely distributed across the brain (Dronkers et al., 2017). The change experienced in the neuroscience community and, specifically, in the language field from a more localizationist to a more connectivist perspective has several implications. A crucial one is the understanding of the importance of brain anatomical connections, which equate to that of cortical regions (Filley & Fields, 2016). One can think of an online purchase as an easy way to exemplify the importance of the integrity of neural connections: when buying something online, it does not matter when or how the product leaves the store, as we will never receive it home if there is a problem in the delivery (e.g. if the carrier loses the package, if it is delivered to the wrong person, etc.). In a similar way, injuries to brain connections can have as dramatic consequences as injuries to the eloquent areas. Another implication is that connectivism relies on extrinsic connections between specialized areas, which implies that the functional role of brain areas largely depends on its connections. Similarly, the properties of the connections also depend on the regions they connect. Therefore, the study of brain connections can be of great relevance for the understanding of the mechanisms of language processing and acquisition in the brain.

But what are we talking about when we say brain connections? The neurons are the basic functional unities of the nervous system (Moore, 2006). The neuron bodies –or somas– are responsible for processing information that are received from other neurons by branched projections called dendrites. In turn, each neuron has a single extension –the axon– that allows it to transmit the signal to the next neural cell. Axons from different neurons that have similar destinations group together forming bundles, which in turn form bigger packs called white matter tracts* (Catani & Thiebaut de Schotten, 2012). Therefore, white matter tracts are just groups of axons that allow the connection between different regions of the brain, no matter how distant

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*In the literature we can find many terms that have been used interchangeably to refer to groups of axons that travel together. Some studies have differentiated the term *stream* to refer to the ensemble formed by one or more white matter tracts together with their origin and termination cortical areas. On the other hand, the terms *tract*, *pathway* or *bundle* have been used interchangeably to refer exclusively to a group of axons with a common path (Sierpowska et al., 2017; Weiller et al., 2011). In this thesis I have also used this distinction.

these regions may be. In fact, these white matter tracts can be classified depending on the proximity and localization of the regions they connect: i) U-fibers are short tracts that connect adjacent gyri; ii) commissural fibers link regions from left and right hemispheres; iii) association fibers connect regions from different lobes within the same hemisphere, and iv) projection fibers connect regions from the cortex with subcortical areas such as the brainstem or the spine (Marco Catani & Thiebaut de Schotten, 2012). No matter their type of connection, two regions linked by a white matter tract are structurally connected. But union can also have functional implications. If two structurally linked regions have been associated with a certain function, it is likely that the white matter pathway connecting them is also related to this function. This is because the axons of said tract will be responsible for the transit of information between those areas. In other words, the white matter tracts represent the structural basis of large-scale cognitive networks (Sha, Schijven, Fisher, & Francks, 2023). Hence, the pathways' origin and termination, as well as their anatomical path per se, can provide information regarding their function. Based on the above stated, the relevance of the study of white matter tracts in the investigation of the bases of LA is obvious and clear. In the next section I make a brief methodological preview to give a quick overview of the main tools we have at our disposal to carry out this purpose.

1.5 Methods for studying white matter

There are several techniques for the study of white matter connectivity. One of the most used methods throughout history has been post-mortem fiber dissection. This was already used in the studies of the first anatomists, namely Galenus or Vesalius (Clarke & O'Malley, 1996), and the improvements achieved over the years related to brain preparation methods make it a very useful technique, especially to unmask anatomical details of the tracts such as the three-dimensional structure or the subcomponents that form the pathways (Martino et al., 2013). Although precise, this technique has the enormous limitation that, by definition, it cannot be performed in vivo. Autoradiography is another option for studying white matter and consists in the use of radioactive tracers to determine the origin and termination of white matter tracts (Cowan, Gottlieb, Hendrickson, Price, & Woolsey, 1972). Although its toxicity prevents its use in humans, it has helped in the advance of comparative and evolutive research, mainly in the investigation of white matter fibers in primates (Schmahmann et al., 2007). Yet another technique used for this purpose is direct electrical stimulation (Hugues Duffau, 2015; Hugues Duffau et al., 2003; Hugues Duffau, Moritz-Gasser, & Mandonnet, 2014). This method consists in electrically stimulating specific white matter pathways in the brain, which causes a temporary stimulation or inhibition of their function. It can be used in both asleep and awake patients, but it is in the latter that changes in behavior secondary to this stimulation can be observed, thus obtaining a causal demonstration of the role of the stimulated white matter tract (Sierpowska et al., 2017). Its major disadvantage,

however, is that it is an invasive technique, as this electrical stimulation is performed intraoperatively (Shekari & Nozari, 2023). Despite their precision and the large amount of information obtained over the years by these techniques, their major drawbacks greatly limit their applicability in humans. This has caused their popularity to decrease in recent years in favor of neuroimaging techniques.

Neuroimaging techniques represent a great alternative to the techniques mentioned so far, as they allow for the study of the human brain in vivo and non-invasively. Their emergence at the end of the 20th century followed by their subsequent improvements, both in the techniques themselves but also in the processing and analysis of images, have caused an enormous revolution in the field (Dronkers et al., 2017). In fact, they have been crucial in achieving our current level of knowledge regarding the anatomy and functions of white matter pathways, especially in the case of structural MRI methods. There is a wide array of neuroimaging methods for studying white matter, from volumetric to tractography techniques. Among the volumetric techniques, ***Voxel-Based Morphometry*** (VBM) has been one of the most popular ones. Although it has been more frequently used for the study of grey matter tissue, some authors have also employed it for the exploration of white matter (Lei et al., 2015). This method consists in obtaining and normalizing structural images and comparing the concentrations or volumes of voxels containing the tissue of interest (white matter, in the case of this thesis), for which the method is usually named *Voxel-Based Analysis*. Then, this data can be compared between two or more groups of images: principally different groups of subjects or different temporal points of the same cohort of subjects (Mechelli, Price, Friston, & Ashburner, 2005). Therefore, the final result would show a comparison of brain volumes between groups of data, indicating significant changes or differences between them (Mechelli et al., 2005). These white matter concentrations or volumes can also be correlated with behavioral measures for a given group (Nenadić, Lorenz, & Gaser, 2021). Another related technique is ***Voxel Lesion-Symptom Mapping*** (VLSM), which also starts from obtaining and normalizing structural images, although in this case it is performed in patients with brain lesions. Said brain lesions are identified and located in the images. In addition, some type of behavioral measure such as performance on a test or task must also be obtained. With these two measures, a univariate regression is applied in each voxel to relate scores of the behavioral measure with brain integrity in said voxel. Therefore, this technique allows us to obtain a final map of the regions related to performance in a task or any other behavioral information (E. Bates et al., 2003).

However, the truly revolutionary advancement of the last few decades has been the use of MR diffusion imaging (dMRI) to investigate white matter pathways. Diffusion of water molecules in the brain is characterized by random –or brownian– motion. Therefore, in the absence of physical boundaries, water diffusion should be equal in all directions in what is known as isotropic

diffusion. This is the case of molecules in cerebrospinal fluid, and to a lesser extent in gray matter, where movement is unconstrained. On the contrary, white matter tissue presents several microscopic boundaries such as axon membranes and myelin sheaths that force water diffusion in some preferential direction, resulting in *anisotropic diffusion* (Alexander, Lee, Lazar, & Field, 2007; Càmara, 2008). One of the most extensively used method for analyzing this data is diffusion tensor imaging, or DTI for short (Craddock et al., 2013; Mori & Zhang, 2006; Mukherjee, Chung, Berman, Hess, & Henry, 2008). With this technique, the magnitude and direction of water diffusion can be calculated at each voxel (Dronkers et al., 2017). This, in turn, allows for the calculation of different metrics –from the data acquired during the displacement in different directions–, being the most common ones in the literature: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) (Shekari & Nozari, 2023). These metrics quantify microstructural properties of white matter tissue and can be used to detect possible damages or to perform correlations with behavioral performance scores (Càmara, 2008). Moreover, DTI can be used to reconstruct white matter pathways non-invasively in a process called *tractography* (Marco Catani, Howard, Pajevic, & Jones, 2002). Tractography approaches are based on the assumption that, if there is certain alignment between two contiguous voxels in the principal direction of diffusion, it is likely they form part of the same pathway (Pajevic & Pierpaoli, 1999). Then, elaborate algorithms allow us to extrapolate and trace the probable fibers contained between different voxels. These tractography algorithms can be generally classified into two categories: deterministic or probabilistic. ***Deterministic algorithms*** assume the main diffusion direction per voxel and creates a single streamline per starting point by linking voxels with similar diffusion directions (D. K. Jones, 2008). This method can be refined by the application of constraints like controlling for a minimum FA value, defining the maximum curvature angle of a streamline or establishing a set of regions of interest (Marco Catani et al., 2002). On the other hand, ***Probabilistic tractography*** traces multiple streamlines per seed voxel, considering different possible trajectories for each tract. Therefore, the final output is a probability map of connections, from which the final tracts can be outlined by applying a probability threshold and/or other restrictions, like the definition of regions of interest (D. K. Jones, 2008). The fundamental differences between these two algorithms inevitably entail diverse strengths and weaknesses in each case. Deterministic tractography is more focused on the anatomical pathway of the fibers, requires lower computational power, and generates faster results with a clearer delineation of tracts. Nevertheless, it is also usually more time consuming, more experimenter biased, and present difficulties in resolving tracking indeterminacies in case of unclear primary diffusion direction (i.e., kissing, crossing, or fanning fibers). Alternatively, probabilistic tractography offers lower operator dependency, less time consumption for the experimenter, and improved sensitivity in uncertain voxels. It also presents downsides like long computation times, less specificity (more false-positive streamlines), less intuitive visualization, or the fact that there

is no broad consensus on a crucial aspect like the appropriate probability threshold to be selected (Lilja et al., 2014). In the last few years, the emergence of new acquisition strategies (e.g., high angular resolution diffusion-weighted imaging or HARDI) and models (e.g., constrained spherical deconvolution or CSD) have been proposed to improve some of the above-stated problems such as more accurately dealing with crossing fibers (Nina F. Dronkers et al., 2017; Tournier, Mori, & Leemans, 2011). This approach for the study of cerebral white matter has allowed us to better understand the origins and terminations of the different tracts, as well as their route and subcomponents (Marco Catani & Thiebaut de Schotten, 2008; Fekonja et al., 2019; Martino et al., 2013). They have also allowed us to obtain information about their macrostructure (e.g. volume, length) and microstructure (e.g. FA, RD), being able to compare these values between groups or detect changes over time either due to learning, injury or plasticity (Roberts, Anderson, & Husain, 2013). But crucially for the present thesis, these methods have allowed us to identify the tracts that might be related to language (either its processing or its acquisition), and hypothesize about their specific functions (Bajada, Lambon Ralph, & Cloutman, 2015; Anthony Steven Dick et al., 2014), as well as to study how lesions in these pathways can cause specific linguistic deficits (Catani & Mesulam, 2008).

1.6 Language-related white matter tracts

Overall, the techniques described in this section, with a particularly relevant role of tractography, have allowed our knowledge about cerebral white matter tracts to experience an enormous growth. In this last section of the introduction, I will present the association fibers that have been associated with language functions. I will describe each tract individually, focusing on their origins and terminations, followed by its ascribed cognitive and linguistic functions. As discussed in the first section of this introduction, current models propose a dual stream for language processing: dorsal stream for sound-to-motor, and ventral for sound-to-meaning mapping (Hickok & Poeppel, 2007). We have also seen in this introduction how some models incorporate these streams as well when trying to explain the bases of LA (Rodriguez-Fornells et al., 2009). However, the concept of stream, as used in these models, refers to both the regions and the connections that are involved in these processes, so they also include the white matter pathways, even if not mentioned explicitly in some cases. Accordingly, the cortical regions and white matter tracts involved in language processing are also usually classified into dorsal and ventral depending on their position in the brain relative to the lateral fissure. The dorsal stream is mainly formed by: the arcuate fasciculus (AF), some of the components of the superior longitudinal fasciculus (SLF), and a more recently described tract called frontal aslant tract (FAT). On the other hand, it is usually considered that the ventral stream is composed mainly by: the inferior longitudinal fasciculus (ILF), the inferior fronto-occipital fasciculus (IFOF), and the uncinate fasciculus (UF), although

some studies also include the extreme capsule (EmC) and the middle longitudinal fasciculus (MdLF) (Catani & Thiebaut de Schotten, 2008; Shekari & Nozari, 2023; see Figure 4).

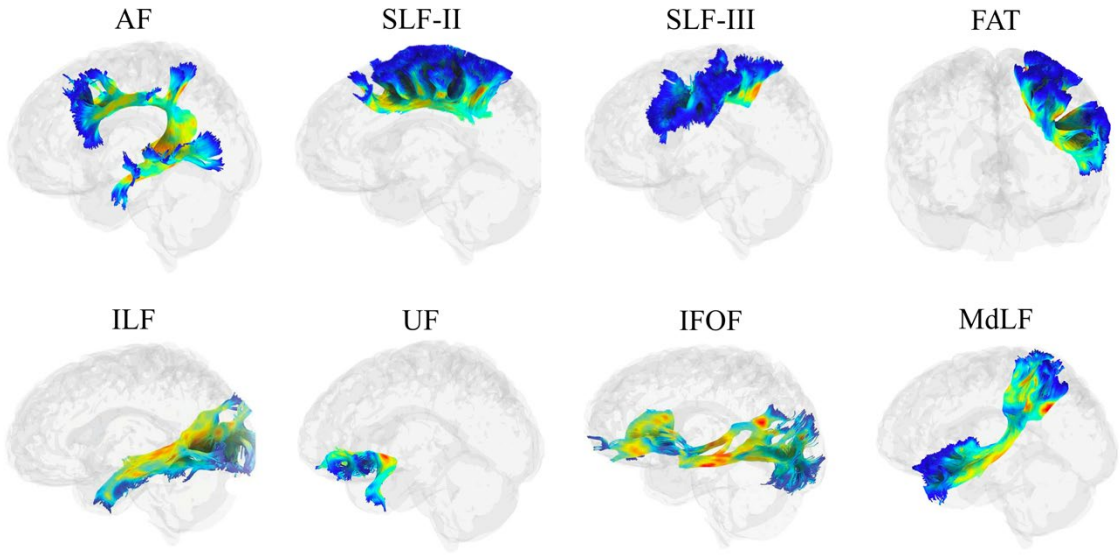

Figure 4. Main language related white matter pathways (adapted from Shekari and Nozari, 2023). The top row shows the main dorsal language tract that include, from left to right, the Arcuate Fasciculus (AF), the Superior Longitudinal Fasciculus-II (SLF-II); the Superior Longitudinal Fasciculus-III (SLF-III) and the Frontal Aslant Tract. The bottom row shows the main ventral language pathways including, also from left to right, the Inferior Longitudinal Fasciculus (ILF), the Uncinate Fasciculus (UF), the Inferior Fronto-Occipital Fasciculus (IFOF) and the Middle Longitudinal Fasciculus (MdLF).

1.6.1 Dorsal tracts

1.6.1.1 Arcuate Fasciculus

The Arcuate Fasciculus (AF) is possibly considered the main tract of the dorsal stream, although there is some controversy regarding its specific anatomical terminations and the subcomponents that form it: some authors propose a dual division into dorsal and ventral components (Berwick, Friederici, Chomsky, & Bolhuis, 2013; Fernández-Miranda et al., 2015), while others propose a triple division into one direct and two indirect segments (Catani, Jones, & ffytche, 2005). Although the different accounts seem to disagree on the number of subparts (A. S. Dick & Tremblay, 2012), the division into direct and indirect segments seems to be widely accepted (Catani et al., 2005). According to this classification and the most accepted descriptions (Catani et al., 2005; Catani & Thiebaut de Schotten, 2008), the AF is formed on the one hand by a main segment –called long or direct segment– which connects the posterior superior temporal (pSTC) and posterior middle temporal cortices (pMTC) with the inferior frontal gyrus (IFG), the middle frontal gyrus (MFG), and the ventral premotor cortex (vPMC). On the other hand, the AF is subdivided into two indirect components: i) the anterior segment, that links the IFG, MFG and vPMC with the inferior parietal lobe (IPL), and ii) the posterior segment, that connects the IPL

with the pSTC and pMTC (Catani et al., 2005; Giampiccolo & Duffau, 2022; Tremblay et al., 2019). Irrespectively of its functions, the long segment of the AF is strongly left-lateralized in most of the population (Catani et al., 2005), the anterior segment appears to be right lateralized, and the posterior segment does not show a particular lateralization pattern (Michel Thiebaut de Schotten et al., 2011). Functionally, the AF has been associated with a wide array of language-related processes, such as auditory processing (Moore, Schaefer, Bastin, Roberts, & Overy, 2017; Tremblay et al., 2019; Vaquero et al., 2021), phonological awareness (Dodson et al., 2018; Yeatman et al., 2011), or reading (M. Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2014; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012). However, the bulk of the literature identify the AF with language production, specifically with naming (Marchina et al., 2011), speech fluency (Karen Chenausky, Paquette, Norton, & Schlaug, 2020; Ivanova, Zhong, Turken, Baldo, & Dronkers, 2021), and nonword repetition (Saur et al., 2008; Sierpowska et al., 2017). Some work has also tried to identify the role of the AF indirect components, pointing to the anterior segment's role in speech fluency (Halai, Woollams, & Lambon Ralph, 2017) and naming (Ivanova et al., 2021), or the posterior segment in language comprehension (Ivanova et al., 2021). Of special relevance for this thesis are the reports that have linked the AF with language learning and acquisition. A longitudinal study reported an association between vocabulary development in children and the microstructure of the left AF (Su, Zhao, et al., 2018). Similarly, the integrity of the left AF has been linked to word learning ability in healthy adult participants (López-Barroso et al., 2013). This same relationship has also been found in patients, namely a child with perinatal stroke (François et al., 2016) and adult individuals with post-stroke aphasia (Coran et al., 2020; Tuomiranta et al., 2014), further corroborating the role of this tract in LA.

1.6.1.2 Superior Longitudinal Fasciculus

The Superior Longitudinal Fasciculus (SLF) connects the parietal and frontal lobes and is generally divided into three different branches: i) the SLF-I is the most dorsal branch of the three and links the superior parietal lobule (SPL) with the superior frontal gyrus (SFG); ii) the SLF-II runs parallel to the long segment of the AF and connects the IPL with the dorsolateral prefrontal cortex (DLPFC); iii) the SLF-III originates in the IPL and terminates in the vPMC (Petrides & Pandya, 1984; Yeterian, Pandya, Tomaiuolo, & Petrides, 2012). The SLF-III as described in the literature is indiscernible from the anterior segment of the AF, and therefore has been related to the same language functions (Janelle, Iorio-Morin, D'amour, & Fortin, 2022; Sierpowska, 2017). Additionally, some studies have described a temporoparietal component of the SLF, the SLF-tp, that would connect the pSTG with the IPL and SPL (Bullock et al., 2019; Kamali, Flanders, Brody, Hunter, & Hasan, 2014). However, similarly to what we described for the SLF-III, its existence is a matter of debate as it overlaps with what we call the posterior segment of the AF (Catani &

Thiebaut de Schotten, 2008; Kamali et al., 2014). As for their functions, the SLF-I is usually described to be related to visuospatial processing and eye-hand coordination, therefore lying beyond the scope of this thesis (Granek, Pisella, Blangero, Rossetti, & Sergio, 2012). Although previous reports do not always distinguish between the SLF branches, when they do, it is often the SLF-III –and sometimes the SLF-II– that are suggested to be related to language functions. There is a body of evidence relating this tract to phonological processing, and more specifically to phonological awareness (Dodson et al., 2018) and word production (McKinnon et al., 2018; Powers et al., 2013; Stark et al., 2019). Furthermore, the SLF has also been suggested to play a role in reading (Bruckert et al., 2019) and syntactic processing (Mills et al., 2013).

1.6.1.3 Frontal Aslant Tract

The Frontal Aslant Tract (FAT) is a quite recently-described pathway that connects the IFG pars opercularis –and on some occasions, triangularis– with the supplementary motor area (SMA) and pre-SMA regions (Catani et al., 2012). It is a left lateralized pathway proposed to have a key role in language (Tremblay & Dick, 2016), especially in speech production (Fujii et al., 2015; Vassal, Boutet, Lemaire, & Nuti, 2014). A link has been established between the integrity of the FAT and verbal fluency or motor execution of speech, as observed in individuals who suffer from stuttering (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016) and patients with Post-Stroke Aphasia (Alyahya, Halai, Conroy, & Lambon Ralph, 2020), Primary Progressive Aphasia (Catani et al., 2013), or non-verbal autism spectrum disorder (Karen Chenausky, Kernbach, Norton, & Schlaug, 2017). Additionally, a recent study proposed that the FAT could be involved in the selection of appropriate motor plans, being related to language in the left hemisphere and domain-general in the right hemisphere (Anthony Steven Dick, Garic, Graziano, & Tremblay, 2019). This framework could explain the evidence linking the FAT to a “stopping” behavior of motor commands (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003) and reconcile conflicting results regarding FAT’s role in linguistic aspects such as syntactic processing (Chernoff, Sims, Smith, Pilcher, & Mahon, 2019; Dragoy et al., 2020; Sierpowska et al., 2015) that have been under debate over the last years.

1.6.2 Ventral tracts

1.6.2.1 Inferior Longitudinal Fasciculus

The Inferior Longitudinal Fasciculus (ILF) is a long association tract that originates in the cuneus, lingual and fusiform gyrus, runs laterally to the fibers of the splenium and the optic radiation and terminates in the anterior temporal lobe (ATL; Catani et al., 2002; Zemmoura, Burkhardt, & Herbet, 2022). Some short fibers do not reach the ATL and instead appear to terminate at the level

of the amygdala and hippocampus (Marco Catani & Thiebaut de Schotten, 2008). Recent descriptions suggest its division into a dorsal component that would originate in the cuneus and a ventral component that would start in the lingual and fusiform gyrus, with both terminating in the ATL (Sali et al., 2018; Zemmoura et al., 2022). Given its occipital origin, it has been repeatedly implicated in visual processing and reading (Grotheer, Yeatman, & Grill-Spector, 2021; Hodgetts et al., 2015; Sarubbo et al., 2015), as well as with orthographic processing (Su, Zhao, et al., 2018; K. Wang et al., 2020). But the ILF, as a component of the language-processing ventral-stream, has also been related to semantic-lexical functions. This relationship was found in several investigations evidencing lower performances in picture naming tasks or increased semantic paraphasias in connected speech tasks in patients presenting ILF lesions, as compared to neurotypical participants (Faulkner & Wilshire, 2020; Griffis, Nenert, Allendorfer, & Szaflarski, 2017; McKinnon et al., 2018; Stark et al., 2019). Moreover, the integrity of the ILF has been related to the success in producing words that are weakly associated with a target word (Nugiel, Alm, & Olson, 2016), a process that requires semantic control. Importantly for this dissertation, the microstructural properties of the ILF have also been linked to contextual learning success in neurotypical adults (Ripollés et al., 2017).

1.6.2.2 Uncinate Fasciculus

The Uncinate Fasciculus (UF) is a hook-shaped tract that originates in anterior regions of the temporal lobe, namely the ATL, the perirhinal and entorhinal cortices and the uncus. These fibers travel through the extreme/external capsule and terminate in the orbitofrontal cortex (OFC), the frontal pole (FP) and the IFG (Briggs et al., 2019; Catani & Thiebaut de Schotten, 2008). This pathway has been consistently associated with emotional processing, and its abnormalities have been observed in several psychiatric disorders (Jung et al., 2020; Travers et al., 2012; J. Zhang et al., 2014). However, the UF has also been associated with several language functions in aphasic patients, specifically to semantic processing, including auditory comprehension, naming, or spontaneous speech, as well as semantic control (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013; Harvey, Wei, Ellmore, Hamilton, & Schnur, 2013; Mirman, Zhang, et al., 2015; B. Zhang et al., 2021). These functions fit with the UF alterations frequently observed in dementia and the semantic variant of PPA (Agosta et al., 2013; Bouchard, Wilson, Laforce, & Duchesne, 2019; Powers et al., 2013; Tu, Leyton, Hodges, Piguet, & Hornberger, 2015). This tract's integrity has also been linked to performance in semantic fluency tasks (Di Tella et al., 2020; C. Papagno et al., 2011; Costanza Papagno et al., 2016) and reading abilities (Nikki Arrington, Kulesz, Juranek, Cirino, & Fletcher, 2017). Of special relevance for this dissertation are the studies that have reported associations between the integrity of the UF and both verbal memory (Christidi et al., 2014; Schaeffer et al., 2014) and verbal learning tasks (Alm, Rolheiser, & Olson, 2016; Ripollés et al., 2017, 2014; Rossi, Cheng, Kroll, Diaz, & Newman, 2017). Additionally, this tract has also

been implicated in reward and punishment processing (Shekari & Nozari, 2023). This is relevant here because successful LA has been shown to have an intrinsic reward value (Ripollés et al., 2017, 2014). Hence, the UF could also have an important role in LA through the regulation of reward-based learning, in general, and in LA specifically, although this association remains to be tested.

1.6.2.3 Inferior Fronto-Occipital Fasciculus

The Inferior Fronto-Occipital Fasciculus (IFOF) is the longest association tract of the brain (Sierpowska, 2017). Its fibers originate in the SPL, the superior and middle occipital gyri, the lingual and the fusiform gyrus, and it runs parallel and medial to the ILF. After going through the extreme/external capsule –dorsally to the UF– this pathway terminates in the IFG, MFG and DLPFC (Catani & Thiebaut de Schotten, 2008; Duffau, 2015). Some recent accounts have also reported temporal terminations of the tract, including the MTG and ITG (Vassal, Pommier, Sontheimer, & Lemaire, 2018). Due to its occipital connections, the IFOF has been repeatedly related to reading processes, along with the ILF (Kumar & Padakannaya, 2019; Nikki Arrington et al., 2017; Zhao, Thiebaut de Schotten, Altarelli, Dubois, & Ramus, 2016). Similarly to the other ventral tracts described so far, the IFOF has also been associated with semantic processing, manifested by picture naming errors following IFOF injury (Griffis et al., 2017) or semantic paraphasias following IFOF intraoperative stimulation (Almairac et al., 2015; Hugues Duffau, 2015; Fernández, Velásquez, García Porrero, de Lucas, & Martino, 2020; Motomura et al., 2018). In line with this, the integrity of the IFOF has been associated with semantic control in the context of conflict resolution during comprehension (Harvey & Schnur, 2015), as well as in the production of weakly-associated words from target terms, along with the ILF (Nugiel et al., 2016). Finally, the microstructural properties of this tract have been associated with success in a novel-language learning task in healthy adults (Ripollés et al., 2014).

1.6.2.4 Middle Longitudinal Fasciculus

The Middle Longitudinal Fasciculus (MdLF) was first reported decades ago (Seltzer & Pandya, 1984) although it has been absent from most of the white matter atlases and related literature until quite recently (Shekari & Nozari, 2023). This could be due to the MdLF being classically considered a part of neighboring tracts such as the AF/SLF or the ILF, meaning that it has not always been considered as an independent bundle in the past (Saur et al., 2008; Shekari & Nozari, 2023). Although there is no consensus regarding its cortical terminations, it is thought to connect the SPL and superior occipital lobe to the STG and ATL (Kalyvas et al., 2020; Shekari & Nozari, 2023). Although its anatomical connections provide theoretical support for its language

involvement (Kalyvas et al., 2020), the few existing studies investigating its role in language processing or learning provide mixed results, with no strong evidence suggesting its essential role in this domain (Blom-Smink et al., 2020; De Witt Hamer, Moritz-Gasser, Gatignol, & Duffau, 2011; Luo et al., 2020).

1.6.2.5 Extreme Capsule

The Extreme Capsule (EmC) is often mentioned in white matter studies, although its anatomical description varies widely, ranging from simply an anatomical space between the claustrum and the insula, a part of other tracts like the IFOF or the UF, or an entirely independent tract. A detailed study from Makris and Pandya (2009) defined the EmC as a tract linking the IPL with the STG and IFG. Given the lack of consensus on its anatomical basis, its function is poorly understood. However, it has been associated with sound processing (Frey, Campbell, Pike, & Petrides, 2008) and auditory comprehension (Wong, Chandrasekaran, Garibaldi, & Wong, 2011). An investigation from Lopez-Barroso and colleagues (2011) showed an association between the microstructural properties of the EmC and speech segmentation abilities under conditions of rehearsal suppression. These results would point to the tract's involvement in language learning when dorsal tracts are not available. In any case, the evidence so far is sparse, and more research is needed in order to confirm the involvement of this bundle in language processing and acquisition.

1.7 Summary

The previous subsections aimed to give a global vision of the white matter tracts that have been previously related to language, as well as the functions that have been attributed to each one. In general terms, we see that there is a vast knowledge about these pathways in relation to linguistic processing. According to the reviewed literature, these tracts follow the distinction proposed for cortical regions in dorsal and ventral streams, the dorsal tracts being the AF, SLF and FAT, and the ventral tracts including the ILF, UF and IFOF (with open debate regarding whether the MdLF and EmC might also be included in this anatomical and functional set). As described for the cortical bases, dorsal white matter tracts are mostly associated in the literature with phonological processing while ventral tracts are usually more related to lexico-semantic processing (Shekari & Nozari, 2023). However, the previous section also shows the lack of conclusive evidence regarding the structural bases of language acquisition (see Figure 5 for a graphical summary). There are only a handful of studies addressing this issue, so the information available in this regard is very limited, both in volume and consistency. In other words, the literature in the field shows great variability, with studies that examine only a specific tract, reports focused on different populations, lack of consistency in anatomical definitions, etc. This limited evidence and open

debate about anatomical and functional descriptions of white-matter underpinnings of LA has been the main motivator of the present thesis. Jointly with my interest to improve our understanding of these LA, STM and other linguistic-related functions in different pathological conditions affecting language functions.

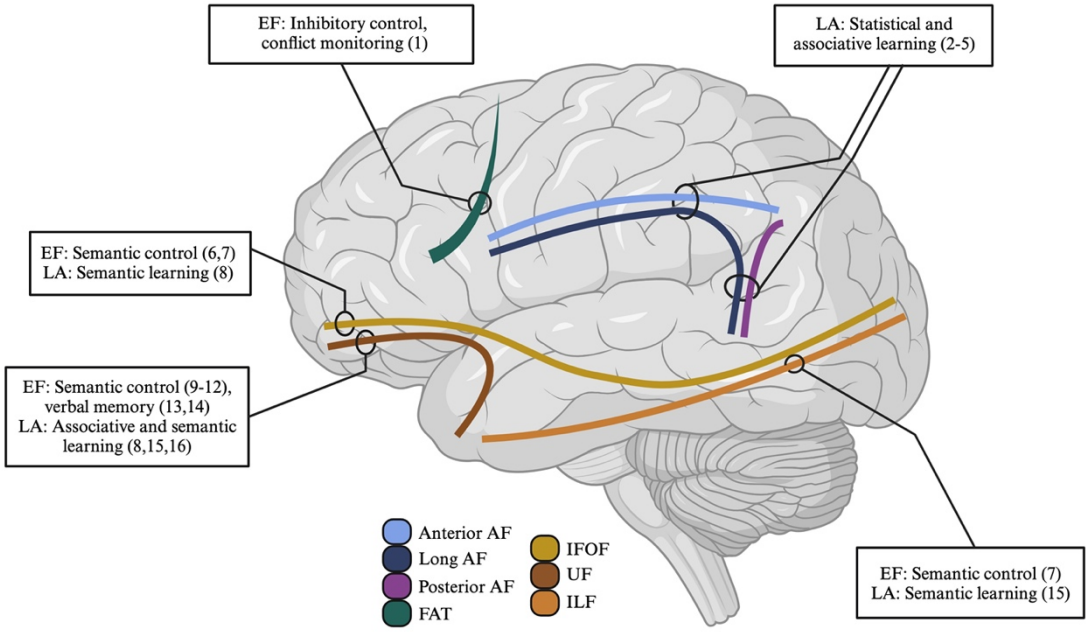

Figure 5. Proposed white matter tracts related to language acquisition and their functions. Summary of the main results found in the literature linking white matter tracts with language acquisition functions or closely related executive functions. Numbers between brackets indicate the reference related to the proposed function for each tract. Abbreviations: EF = executive function, LA = language acquisition, AF = arcuate fasciculus, FAT = frontal aslant tract, IFOF = inferior fronto-occipital fasciculus, UF = uncinate fasciculus, ILF = inferior longitudinal fasciculus. References: [1] Dick et al., 2019; [2] Coran et al., 2020; [3] Francois et al., 2016; [4] López-Barroso et al., 2013; [5] Tuomiranta et al., 2014; [6] Harvey & Schnur, 2015; [7] Nugiel et al., 2016; [8] Ripollés et al., 2014; [9] Fridriksson et al., 2013; [10] Harvey et al., 2013; [11] Mirman et al., 2015; [12] Zhang et al., 2021; [13] Christidi et al., 2014; [14] Schaeffer et al., 2014; [15] Alm et al., 2016; [16] Ripollés et al., 2017. Figure generated with Biorender.com

Chapter 2 - Research aims and hypotheses

Chapter 2 - Research aims and hypotheses

The studies reviewed in the introduction of this dissertation provide a detailed picture of the mechanisms and neural bases of language acquisition. However, our knowledge is mainly restricted to cortical regions related to LA, while the role of the different white matter tracts in this process is scarce and inconclusive. Brain connections play a crucial role in any cognitive process, including LA, as highlighted in the previous chapter. Hence, the main objective of this thesis was to identify the main white matter tracts involved in LA. The sparse previous studies regarding structural white matter connectivity of LA indicate that the entire language-related structural connectivity network is necessary for successful LA (see Rodriguez-Fornells et al., 2009 for a review). Therefore, our hypothesis was that all the main language-related white matter tracts would be involved in the LA process, albeit with different roles. To test this, DTI and deterministic tractography were used in different studies to characterize the main language-related white matter tracts in vivo in different populations. Then, the white matter tract's characteristics were associated with different LA-related performances in PLI. This research aim was directly tackled in studies 1, 3 and 4, but was also indirectly examined in study 2. In Study 1 ('*Structural connectivity in ventral language pathways characterizes non-verbal autism'*), the white matter tracts that could have a critical role in the acquisition of a first language were investigated. To that end, the language-related white matter pathways were dissected and compared, in terms of its macro and microstructure, between three groups: non-verbal ASD (nvASD), verbal ASD (vASD) and neurotypical children. In Study 2 ('*A deficit in semantic word learning in Huntington's Disease'*), the involvement of the basal ganglia and the frontostriatal tracts in LA was discussed. In this experiment, we adapted and administered a well-known contextual word learning (CTXL) task previously used in young neurotypical adults (Mestres-Missé et al., 2014) to people with Huntington's Disease (HD) and Neurotypical Controls. Although neuroimaging data was not collected in this study, the characteristic alteration of HD at the striatal level could provide clues about the role of this subcortical structure –and its connections– with respect to LA processes. Study 3 ('*Impaired semantic word learning in primary progressive aphasia'*) examined the involvement of the main language-related white matter tracts in LA. In this study, a CTXL task was administered to individuals with Primary Progressiva Aphasia (PPA) and Neurotypical Controls. Moreover, this performance was related to the white matter pathways' characteristics. Finally, we aimed to explore the structural bases of verbal Short-Term Memory (vSTM) in aphasia. As presented in the introduction, vSTM is essential for success in the LA process. However, the white matter tracts supporting this critical process have not been properly defined in PSA. Given the importance of vSTM in LA, in **Study 4** ('*The right uncinate fasciculus supports verbal short-term memory in aphasia*') we recruited a sample of 19 individuals with Post Stroke Aphasia (PSA) that completed vSTM tests. We then dissected and characterized the main

language white matter bundles and studied the relationship between their structural integrity and vSTM abilities.

The studies included in this thesis examined populations with different language disorders, considering the multiple advantages that the study of PLI provides, as previously described: theoretical gains combined with possible clinical transference in the form of better characterization, diagnosis, treatment, and/or prognosis of patients. Different types of language impairments are rooted in different neurobiological alterations, causing different cognitive consequences. That is why addressing the same process –LA– by observing the brain under different impairments should allow us to obtain richer perspectives, gaining insights on diverse aspects of said process. For that reason, this dissertation is composed by four studies that have tried to explore the bases of LA by investigating four different language impairments, namely Autism Spectrum Disorder (ASD), Huntington's Disease (HD), Primary Progressive Aphasia (PPA), and Post-Stroke Aphasia (PSA). This approach allowed us to set a secondary objective: to identify potential structural differences present in the studied clinical populations that could explain the differences observed in LA performance when compared to neurotypical controls. Our hypothesis was that different LA impairment could be related to different structural alterations. This aim was adressed in all the studies conforming this thesis, as different language impairments were examined in each of them and the corresponding LA impairment was related to the specific structural alterations present in each case. In Study 1, we hypothesized that the complete disruption of LA ability observed in nvASD might be accompanied by global structural anomalies in the language network, affecting both dorsal and ventral white matter tracts. In study 2, any possible semantic learning impairment found in HD might be related with its characteristic striatal degeneration and a frontostriatal connectivity alteration. In Study 3, we wanted to investigate the structural bases related to the PPA participants' accuracy in our LA task. Our hypothesis was that the verbal learning capacity of PPA individuals should be affected, in comparison with neurotypical controls. Furthermore, we speculated that performance on this task could be related to the integrity of both dorsal and ventral white matter tracts, given that the learning success depended on subjects being able to extract meanings from context, but also to link those meanings with new word forms. Finally, this secondary aim was examined in Study 4, in which we explored the tracts responsible for a possible vSTM deficit observed in PSA patients. Our hypothesis in that specific case was that the impairment in vSTM present in individuals with PSA could be associated with the integrity of tracts with terminations in temporoparietal and frontal regions, which had been previously described as important vSTM underpinnings (Friederici, 2015; Hickok and Poeppel, 2007).

The research aims described above were explored through the 4 studies included in this thesis. Different aspects of the LA process were investigated from different perspectives and by studying different populations with language disorders, in order to obtain a more global and complete perspective on the structures involved in this process.The table below provides a summary of the principal aspects and traits of the studies included in this thesis, which will be presented individually in the following chapter.

		Study 1	***Study 2***	***Study 3***	***Study 4***
Measures obtained	DTI	✓		✓	✓
	Behavioral		✓	✓	✓
Process evaluated	LA	✓	✓	✓	
	vSTM		✓		✓
Population studied		nvASD	HD	PPA	PSA

Table 1. Summary of the principal aspects of each study. Summary of the main aspects evaluated in each study, including the measures obtained, the processes evaluated, and the population studied. Abbreviations: DTI = Diffusion Tensor Imaging; LA = Language Acquisition; vSTM = verbal Short-Term Memory; nvASD = non-vernal Autism Spectrum Disorder; HD = Huntington's Disease; PPA = Primary Progressive Aphasia; PSA = Post-Stroke Aphasia.

Chapter 3 – Results

3.1 Study 1: Structural connectivity in ventral language pathways characterizes non-verbal autism

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Abstract

Language capacities in autism spectrum disorders (ASD) range from normal scores on standardized language tests to absence of functional language in a substantial minority of 30% of individuals with ASD. Due to practical difficulties of scanning at this severe end of the spectrum, insights from MRI are scarce. Here we used manual deterministic tractography to investigate, for the first time, the integrity of the core white matter tracts defining the language connectivity network in nonverbal ASD (nvASD): the three segments of the arcuate (AF), the inferior fronto-occipital (IFOF), the inferior longitudinal (ILF) and the uncinate (UF) fasciculi, and the frontal aslant tract (FAT). A multiple case series of nine individuals with nvASD were compared to matched individuals with verbal ASD (vASD) and typical development (TD). Bonferroni-corrected repeated measure ANOVAs were performed separately for each tract *–Hemisphere (2:Left/Right) x Group (3:TD/vASD/nvASD)*. Main results revealed (i) a main effect of group consisting in a reduction in fractional anisotropy (FA) in the IFOF in nvASD relative to TD; (ii) a main effect of group revealing lower values of Radial Diffusivity (RD) in the long segment of the AF in nvASD compared to vASD group; and (iii) a reduced volume in the left hemisphere of the UF when compared to the right, in the vASD group only. These results do not replicate volumetric differences of the dorsal language route previously observed in nvASD, and instead point to a disruption of the ventral language pathway, in line with semantic deficits observed behaviourally in this group.

1. Introduction

Non- or minimally verbal individuals with autism (nvASD) belong to the low-functioning section of autism spectrum disorder (ASD). They are defined by a severe expressive language deficit, which limits their spoken language acquisition to a handful of single words, with no compensation on the part of sign or written language (Tager-Flusberg & Kasari, 2013). Current insights from magnetic resonance imaging are minimal and largely limited to two studies using diffusion tensor imaging to assess white matter (WM) structural connectivity, mainly focused on the exploration of WM tracts linked to mapping auditory information to articulatory motor representations. One of these studies revealed a reversal of a neurotypical left-right asymmetry of the arcuate fasciculus (AF) in four out of five nonverbal children with ASD (Wan, Marchina, Norton, & Schlaug, 2012). Similarly, when assessing treatment-based change in speech production of 10 minimally verbal children with ASD, an improvement during therapy was related to the integrity of both the left AF and right frontal aslant tract (FAT) (Karen Chenausky et al., 2017). Further in line with this evidence, at least a subset of nvASD children have been reported to show childhood apraxia of speech (KV Chenausky, Brignell, Morgan, & Tager-Flusberg, 2019), a developmental motor speech impairment (ASLHA: American Speech-Language-Hearing Association, 2021).

Language deviance in children and adults with nvASD, however, is not confined to expressive language. Language comprehension also falls far below the one expected from their chronological age (CA), and some evidence suggests that expressive and receptive language levels correlate in nvASD (Chenausky, Brignell, Morgan, & Tager-Flusberg, 2019; Hartley, Trainer, & Allen, 2019; Pickles, Anderson, & Lord, 2014; Slušná, Rodríguez, Salvadó, Vicente, & Hinzen, 2021). By definition, furthermore, nvASD are not characterized merely by a speech production deficit, but more broadly by an expressive language deficit, which as such reaches beyond the vocal-auditory modality. In the present study, therefore, we aimed to provide the first characterization in nvASD of the fronto-temporal language network as a whole.

This language network distributes information along both dorsal and ventral processing streams (Friederici, 2011; C. J. Price, 2012; Skeide & Friederici, 2016). Broadly, the dorsal pathway is argued to support sound-to-motor mapping, that is, the mapping of auditory speech

sounds to articulatory representations, while the ventral pathway subserves sound-to-meaning mapping, i.e., extracting meaning from auditory speech sounds (Hickok & Poeppel, 2004). Structurally, the dorsal stream incorporates the superior longitudinal fasciculus (SLF)–AF complex, often referred to as SLF/AF, which can be segregated into one direct and two indirect segments (Catani et al., 2005). The SLF/AF underpins sensorimotor processes during speech production and perception (Hickok & Poeppel, 2007; J. P. Rauschecker & Scott, 2009) and is also argued to support higher-level syntactic processes (Friederici, 2015). In addition, the FAT contributes to the dorsal stream with a function argued to be specific to speech production (Marco Catani et al., 2013) or speech-specific cognitive control processes (Dick et al., 2014). Within the ventral processing stream, the inferior fronto-occipital fasciculus (IFOF) is regarded as a crucial pathway subserving semantic processes (H. Duffau et al., 2005; Saur et al., 2008). Running laterally to the IFOF, the inferior longitudinal fasciculus (ILF) has also been hypothesized to aid semantic processing, namely lexical retrieval (Herbet, Moritz-Gasser, Lemaitre, Almairac, & Duffau, 2019; Shin et al., 2019). Finally, the uncinate fasciculus (UF) potentially hosts local phrase structure building (Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006) and might be recruited as an indirect pathway for semantics-related processes (H. Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Harvey et al., 2013).

In the present study, we used manual deterministic tractography to reconstruct the entire aforementioned structural language connectome, comprising the IFOF, UF, FAT, ILF, and the three segments of the AF (long segment, anterior segment, posterior segment), in a case series of 9 nvASD children and adolescents. While this approach is highly labor-intensive and difficult to pursue in large sample sizes, smaller samples provide an opportunity to allow for an individualized approach to the neuroanatomy of each participant (López-Barroso et al., 2013), and the combination of dissection proposals from different authors for the selected tracts (Marco Catani & Thiebaut de Schotten, 2008; Fekonja et al., 2019). After reconstructing these pathways, we estimated their WM macro and micro-structural characteristics by extracting their corresponding tract volume, fractional anisotropy (FA) and radial diffusivity (RD) measures bilaterally. Volume is a white matter macrostructure measure thought to reflect intrinsic

characteristics like fiber-packing, myelin sheath state or tract-surrounding vasculature and glial architecture (Vaquero et al., 2021). In terms of microstructure, several diffusion measures can be extracted from DW-MRI. FA is probably the most used one [compared to other less sensitive measures such as MD (Winston, 2012)] and, like volume, it has been showed to be very sensitive to individual differences (Vaquero, Rodríguez-Fornells, & Reiterer, 2017). FA reflects the degree of anisotropy as denotes the ratio of the variance of the eigenvalues to their mean (Winston, 2012) and can be modulated by several factors such as axon geometry (axon diameter and axonal count), fiber organization and coherence, myelination, or membrane permeability (Friedrich et al., 2020; D. K. Jones, Knösche, & Turner, 2013; Winston, 2012; Zatorre, Fields, & Johansen-Berg, 2012). However, summary parameters may not represent the full picture as changes along various directions can remain uncovered and it might not allow to determine the direction of change in case of reduction or increase in anisotropy (Aung, Mar, & Benzinger, 2013). Therefore, we also extracted radial diffusivity (RD), which has received a growing interest in recent years (Elmer et al., 2019; Ripollés et al., 2017) and can provide better structural details of the state of the axons and myelin (Aung et al., 2013). RD has been related to several biological factors such as number of axons and axon density and, specially, to the myelination degree (with a demyelination related to increased RD values) (Ripollés et al., 2017; Song et al., 2005; Zatorre et al., 2012). Since myelination as reflected in RD values can serve as indicator of the efficiency in the action potentials' conduction along WM pathways, RD could be seen as an index of proper brain/cognitive processing for the tracts studied (Fields, 2008; Ripollés et al., 2017).

To obtain benchmarks of the tracts' macro- and microstructural measures, we also explored 9 typically developing (TD) and 9 verbal children with ASD (vASD), obtained from an online ASD neuroimaging database (ABIDE II), pair-matched on sex, age and handedness with our locally recruited group of nvASD. We hypothesized structural alterations in both ASD groups, showing deviance in the neural organization of language within both the dorsal and ventral streams. This was based on widespread structural anomalies along both of these routes previously documented in vASD cohorts (Travers et al., 2012; Yang et al., 2017). In particular, there have been reports of a loss of hemispheric lateralization of the AF (Fletcher et al., 2010; Joseph et al.,

2014; Liu et al., 2019), and of aberrant WM integrity in the UF associated with socio-affective deficits (Y. Li et al., 2019; Samson et al., 2016), while some studies have also pointed to structural alterations in the IFOF and ILF (Aoki, Abe, Nippashi, & Yamasue, 2013; Jou et al., 2011). By comparing nvASD to both a neurotypical and a vASD group, we expected that a pattern continuous with that of vASD, but potentially more extended, might emerge in the more severe nvASD, though a differential pattern specific to nvASD could also transpire.

2. Methods and Materials

2.1 Ethics approval

This study was approved by the corresponding institutional review board (CEIC Fundació Sant Joan de Déu; PIC-99-17). Written informed consent was obtained from legal guardians of all participants.

2.2 Participants

Nine non- or minimally verbal school-aged children and adolescents diagnosed with ASD (nvASD, 3 females, mean age = 12.5 ± 3.23) were recruited from special schools in Barcelona, Spain. Recruitment criteria included: (a) a parent / center-reported ASD diagnosis confirmed during recruitment via the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2003); (b) an absence of phrase-level functional speech. To compare this sample with benchmarks across TD and verbal ASD (vASD), a database collected at the San Diego State University (SDSU) was used. Specifically, we included two control groups consisting of (i) nine typically developing (TD) children, and (ii) nine vASD children matched on age, sex and handedness. Recruitment criteria for vASD consisted of a clinical diagnosis of ASD confirmed by the ADIR-R, ADOS, and a DSM-5-based clinical judgment, while TD participants required a parent-reported absence of personal / family history of ASD or other neurological or psychiatric conditions. See Table 1 for demographic and neuropsychological data from all three groups.

	TD Mean ± SD (n = 9)	**vASD Mean ± SD (n = 9)**	**nvASD Mean ± SD (n = 9)**	***p* value**
Demographic information				
Sex (Male/Female)	6/3	6/3	6/3	1.000
Handedness (Right/Left)	8/1	8/1	8/1	1.000
Age at MRI acquisition (Years;Months)	12;6 ± 3.49	12;8 ± 3.07	12;6 ± 3.23	0.992
Neuropsychological profile				
Verbal Mental Age (VMA)/IQ	110.33 ± 10.33	93.56 ± 13.34	24.25 ± 15.74	--
Non-verbal IQ	108.44 ± 8.69	104.56 ± 16.38	63.75 ± 16.91	--
Diagnostic score (ADOS)	--	15.11 ± 2.76	17.88 ± 3.64	--

Table 1 Demographic and neuropsychological participant profile – Data are means ± SD unless otherwise stated. Between-group differences were explored using X^2-tests for sex and handedness and one-way ANOVA for age at MRI acquisition. Statistical tests confirmed the lack of significant different across the three groups. ***Neuropsychological profile –*** The neuropsychological tests applied were different for the three groups due to their intrinsic characteristics. Tests administered were: Verbal Mental Age (VMA)/IQ – Peabody Picture Vocabulary Test-III (PPVT-III) in nvASD, Wechsler Abbreviated Scale of Intelligence in vASD and TD; Non-Verbal IQ – Leiter International Performance Test-Revised (Leiter-R) in nvASD, Wechsler Abbreviated Scale of Intelligence in vASD and TD; ADOS – Autism Diagnostic Observation Schedule-2/-Adapted (ADOS-2/ADOS-A) in nvASD and vASD. Abbreviations: TD = Typically development; vASD = Verbal Autism Spectrum Disorder; nvASD = Non-verbal Autism Spectrum Disorder; IQ = intelligence quotient; MA = mental age; ADOS = Autism Diagnostic Observation Schedule.

2.3 MRI acquisition

Non-verbal ASD participants were scanned under anaesthesia, as approved by the corresponding institutional review board (CEIC Fundació Sant Joan de Déu; PIC-99-17), on a Philips Ingenia 3T scanner using a 64-channel head coil at the Sant Joan de Déu Hospital, Barcelona. Diffusion-weighted images (DWI) were acquired with a spin-echo echo-planar imaging (EPI) sequence (TR = 10100 ms, TE = 102 ms, 64 axial slices, 36 directions, 90° flip angle, slice thickness = 2.1 mm, FOV = 23 cm, acquisition matrix = 112 x 112, voxel size = 2.05 mm3) with three non-diffusion (b = 0s/mm2) and 36 diffusion weighted volumes (b = 1250 s/mm2). Data from TD and vASD subjects were collected on a GE 3T Discovery MR750 scanner using an 8-channel head coil (UCSD–CFMRI). DWI were acquired with an EPI sequence (TR = 8500 ms, minimum TE by

scanner protocol, 68 axial slices, 61 directions, slice thickness = 2.0 mm, FOV = 24 cm, acquisition matrix = 128 x 128, voxel size = 2.05 mm3) with one non-diffusion (b = 0 s/mm2) and 61 diffusion weighted volumes (b = 1250 s/mm2).

2.4 MRI preprocessing

A visual inspection was performed by an expert for all data prior to the preprocessing to ensure the absence of any major artifact (due to acquisition errors, movement or others) that could not be corrected during the subsequent processing steps. All images were pre-processed using FMRIB Software Library (FSL www.fmrib.ox.ac.uk/fsl/fdt) and Diffusion Toolkit software (DTK) (R. Wang, Wedeen, & Athinoula, 2015). DWI were processed as follows: (i) eddy-current correction using FMRIB's Diffusion Toolbox (FDT), part of FMRIB Software Library (FSL www.fmrib.ox.ac.uk/fsl/fdt); (ii) brain extraction using FSL's Brain Extractor Tool (S. M. Smith, 2002; S. M. Smith et al., 2004; Woolrich et al., 2009) with 0.3 as threshold value; (iii) rotation of the b-vectors; (iv) reconstruction of the diffusion tensors using DTK (Wang et al., 2015); and (v) whole-brain deterministic tractography using DTK with 35 degrees as maximum curvature and a minimum FA threshold of 0.2.

2.5 Tract dissections

Manual deterministic tractography was performed focusing on the five main language-related tracts: arcuate (AF), inferior fronto-occipital (IFOF), inferior longitudinal (ILF), uncinate (UF) fasciculi, and frontal aslant tract (FAT). Tracts were dissected for each participant in native space, in both hemispheres, using Trackvis software (v.0.6.0.1, http://trackvis.org/) by manually placing Regions of Interest (ROI) as identified in previous reports (Catani & Thiebaut de Schotten, 2008; Fekonja et al., 2019).

AF. The three segments of the AF were dissected using three ROIs drawn in a single slice as described in previous studies (Marco Catani et al., 2005; López-Barroso et al., 2013): a first ROI was delineated in the coronal view encompassing the fibers going to the inferior frontal gyrus

(IFG) (including BA44 and 45); a second ROI was drawn in the axial plane covering the WM fibers traveling to the superior temporal gyrus; finally, a third ROI was depicted on the sagittal view, covering supramarginal and angular gyri. These ROIs were combined to reconstruct the three subdivisions of the AF: the long (fronto-temporal), the anterior (fronto-parietal), and the posterior (temporo-parietal) segments.

FAT. To dissect the frontal aslant tract, two ROIs were delineated: the first was a spherical ROI of radius 8 mm located in the IFG and the second one was a single slice ROI placed in the WM of the superior frontal gyrus, encompassing fibers traveling to the Supplementary Motor Area (SMA) and pre-SMA (Catani et al., 2013).

ILF, UF & IFOF. For the delineation of the WM pathways supporting the ventral stream for language processing (i.e., ILF, IFOF and UF) (Hickok & Poeppel, 2007; J. P. Rauschecker & Scott, 2009), we used the combination of four ROIs according to previous publications (Catani & Thiebaut de Schotten, 2008; Fekonja et al., 2019). The first ROI was placed axially at the level of the anterior temporal lobe (temporal ROI) spreading throughout an average of 5 slices; the second one on the anterior floor of the external/extreme capsule covering an average of 3 slices (frontal ROI); a third one on the region located between the occipital and temporal lobe (occipital ROI); and a fourth spherical ROI of radius 6.5 mm was placed in the middle temporal region, anterior to the radiation of the corpus callosum (temporoccipital ROI). To define each of the tracts of interest, we applied a two-ROI approach: ILF was comprised by fibers going through the temporal and occipital ROIs; streamlines going through both anterior and frontal ROIs were considered as part of the UF; finally, the fibers crossing the frontal and temporoccipital ROIs formed the IFOF (following Fekonja's method) (Fekonja et al., 2019).

Fekonja's method of dissection was selected here for reconstructing the IFOF because we found it to be more permissive in the inclusion of fibers than other methods, generating a more plausible outcome for our type of data, processed following a diffusion tensor kind of analysis (as opposed to higher resolution data that could be processed using spherical deconvolution methods, for instance). Nonetheless, and as stated in the main text, we additionally followed the Catani and

Thiebaut de Schotten's (2008) approach, which defines the IFOF as the fibers travelling through the frontal and occipital ROIs as described above. As expected, both dissection approaches generated similar results in our analyses. See the Online Resource 1 for details and comparison of the ANOVA test performed with the data extracted using each type of IFOF reconstruction. Finally, artefactual fibers, if present in any of the tracts / hemispheres, were removed using exclusion ROIs, as is standard practice in manual reconstructions (Elmer et al., 2019; Vaquero et al., 2021).

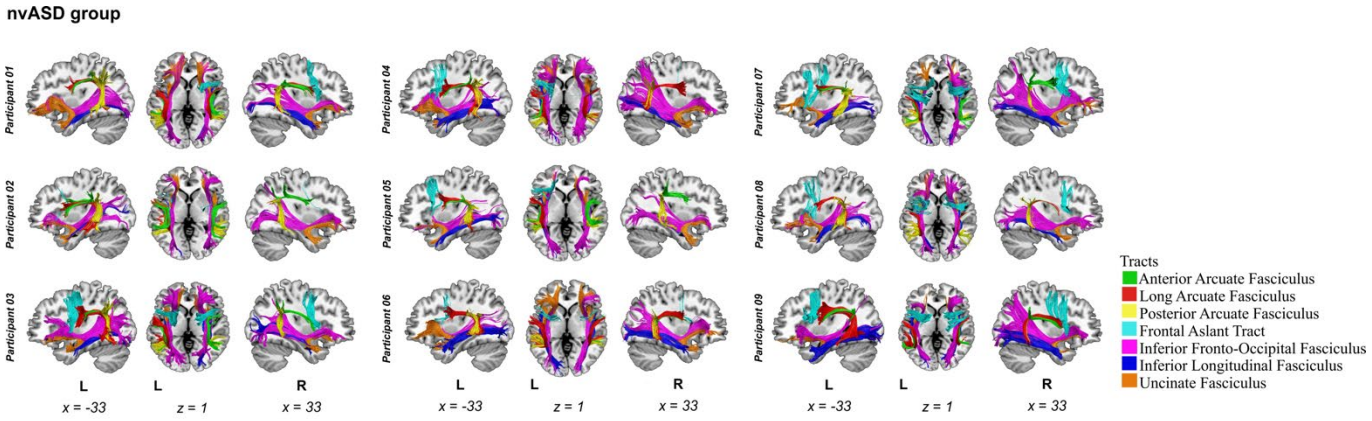

Figure 1 – Dissections of nvASD participants
Manual deterministic tractography reconstructions from all participants of the nvASD group. Tracts reconstructed were the three segments of the arcuate fasciculus (AF) [Green = anterior, red = long, yellow = posterior segments], Frontal Aslant tract (FAT) [Cyan], Inferior Frontal Occipital Fasciculus (IFOF) [Purple], Inferior Longitudinal Fasciculus (ILF) [Dark blue] and Uncinate Fasciculus (UF) [Orange]. Abbreviations: L, left. Montreal Neurological Institute space coordinates of the structural template slices are specified at the bottom of the image. Figure adapted from Olivé et al., 2022.

In order to determine the microstructural measures to include in the main analyses, the whole brain's fractional anisotropy (FA), radial diffusivity (RD), mean diffusivity (MD) and axial diffusivity (AD) values were extracted for each participant. Pearson correlations were then performed between all whole-brain microstructural measures (FA, MD, RD and AD) of all participants. Significant high correlations were found between all three directional microstructural measures: MD and RD ($r = 0.972$, $p < 0.001$), MD and AD ($r = 0.974$, $p < 0.001$), and AD and RD ($r = 0.894$, $p < 0.001$). By contrast, FA did not significantly correlate with any of the other three measures: MD ($r = -0.015$, $p = 0.939$); AD ($r = 0.193$, $p = 0.334$); RD ($r = -0.228$, $p = 0.252$). Based on these results, in previous language-related studies (Elmer et al., 2019; Ripollés et al., 2017), and in order to avoid redundancy, we focused only on one of the directional

measures: RD, in addition to FA and volume, as our final measures of interest. As previously stated, dissections were performed in each participant's native space. In order to control for potential variations in total brain volume, tract volume values were normalized by dividing each tract volume by the total WM volume (from the native space FA maps) for each participant. These normalized volume values were the ones included in the between-group comparison analyses.

The dissections for all participants of the nvASD group are given in Figure 1 and dissections of the vASD and TD participants can be found in the Online Resource 5. For visualization purposes, rendering of the streamlines was performed using the 'tube' render option of TrackVis with a radius of 0.15 mm. Examples of ROI placement are depicted in Figure 2.

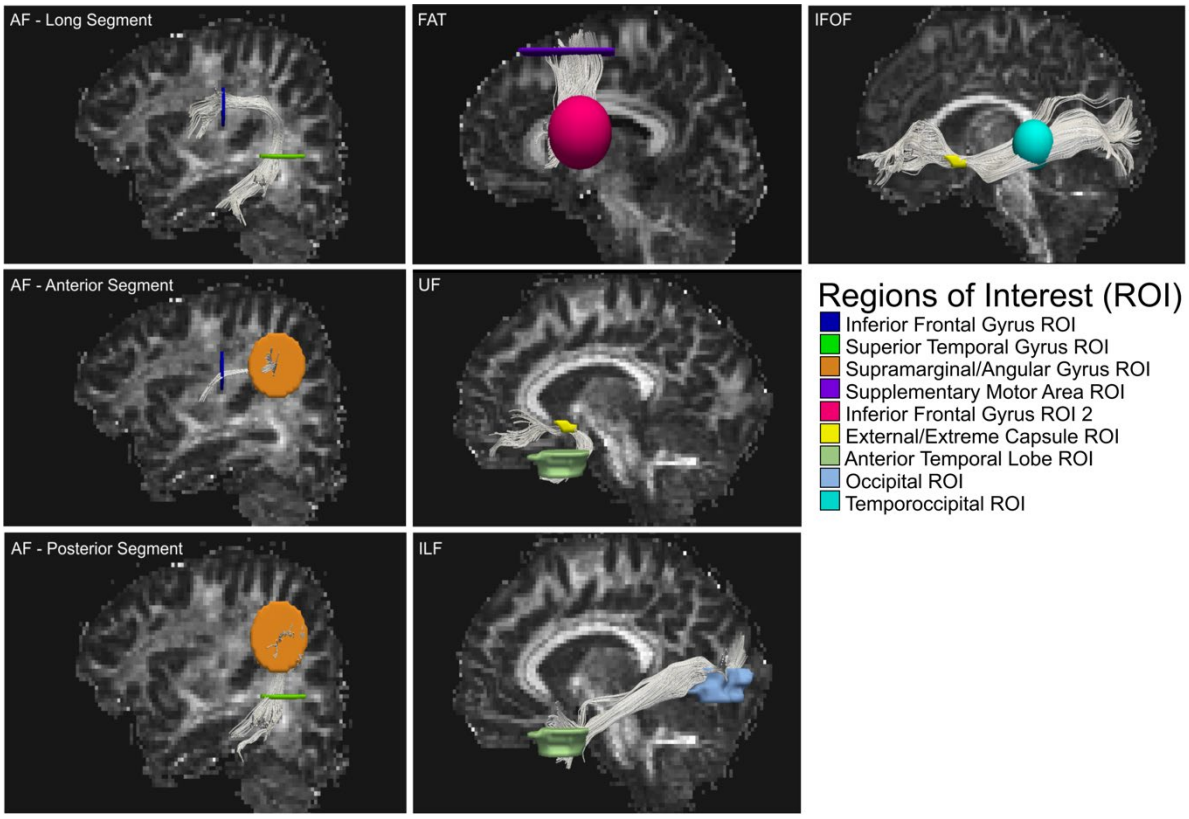

Figure 2 – Regions of Interest placement examples
Regions of Interest (ROI) placements for manual deterministic tractography reconstructions of the selected tracts. Tracts reconstructed were the three segments of the arcuate fasciculus (AF), Frontal Aslant tract (FAT), Uncinate Fasciculus (UF), Inferior Longitudinal Fasciculus (ILF) and Inferior Frontal Occipital Fasciculus (IFOF). Figure adapted from Olivé et al., 2022.

2.6 Statistical analysis

Statistical analyses were performed using IBM SPSS software (v25.0). Hemisphere (2: Left/Right) x Group (3: TD / vASD / nvASD) repeated measures ANOVAs were performed separately for each tract (i.e., AF, FAT, IFOF, ILF, UF) and WM measure (volume, FA, RD), resulting in 15 ANOVAs (5 tracts per 3 measures). Bonferroni correction for multiple comparisons at $p < 0.005$ was applied and only results with a *p*-value below this threshold will be presented below; for uncorrected trends see Online Resources 2, 3 and 4.

3. Results

ANOVA results are detailed in the Online Resources 2, 3 and 4, and significant results and distributions are depicted in Figure 3.

Tract volume. A main effect of hemisphere was observed for the volume of the long ($F(1,24) = 40.982$, $p < 0.001$) and posterior ($F(1,24) = 42.485$, $p < 0.001$) segments of the AF, both showing larger volumes in the left compared to the right AF across all groups. Importantly, an interaction of hemisphere and group was observed in the UF ($F(2,24) = 9.997$, $p < 0.001$), showing a reduced volume in the left compared to the right UF, in the vASD group only, with Bonferroni corrected *post-hoc* tests confirming this effect (volume differences between left and right UF in vASD: $F(1,24) = 12.486$, $p = 0.002$; in TD: $F(1,24) = 4.080$, $p = 0.055$; in nvASD: $F(1,24) = 3.469$, $p = 0.075$).

Fractional Anisotropy. A main effect of hemisphere was found in the ILF ($F(1,23) = 63.097$, $p < 0.001$), where larger FA values were found in the left compared to the right hemisphere across the three groups. Moreover, a main effect of group was encountered in the IFOF ($F(2,24) = 8.062$, $p = 0.002$), showing a gradual tendency to decrease in FA in both ASD groups compared to TD individuals (TD > vASD > nvASD). *Post hoc* comparisons (Bonferroni corrected) showed that this effect was driven by differences between TD and nvASD groups ($F(2,24) = 8.062$, $p = 0.002$), whereas the comparisons between TD and vASD ($F(2,24) = 8.062$, $p = 0.061$) or between vASD and nvASD ($F(2,24) = 8.062$, $p = 0.448$) groups did not reach significance.

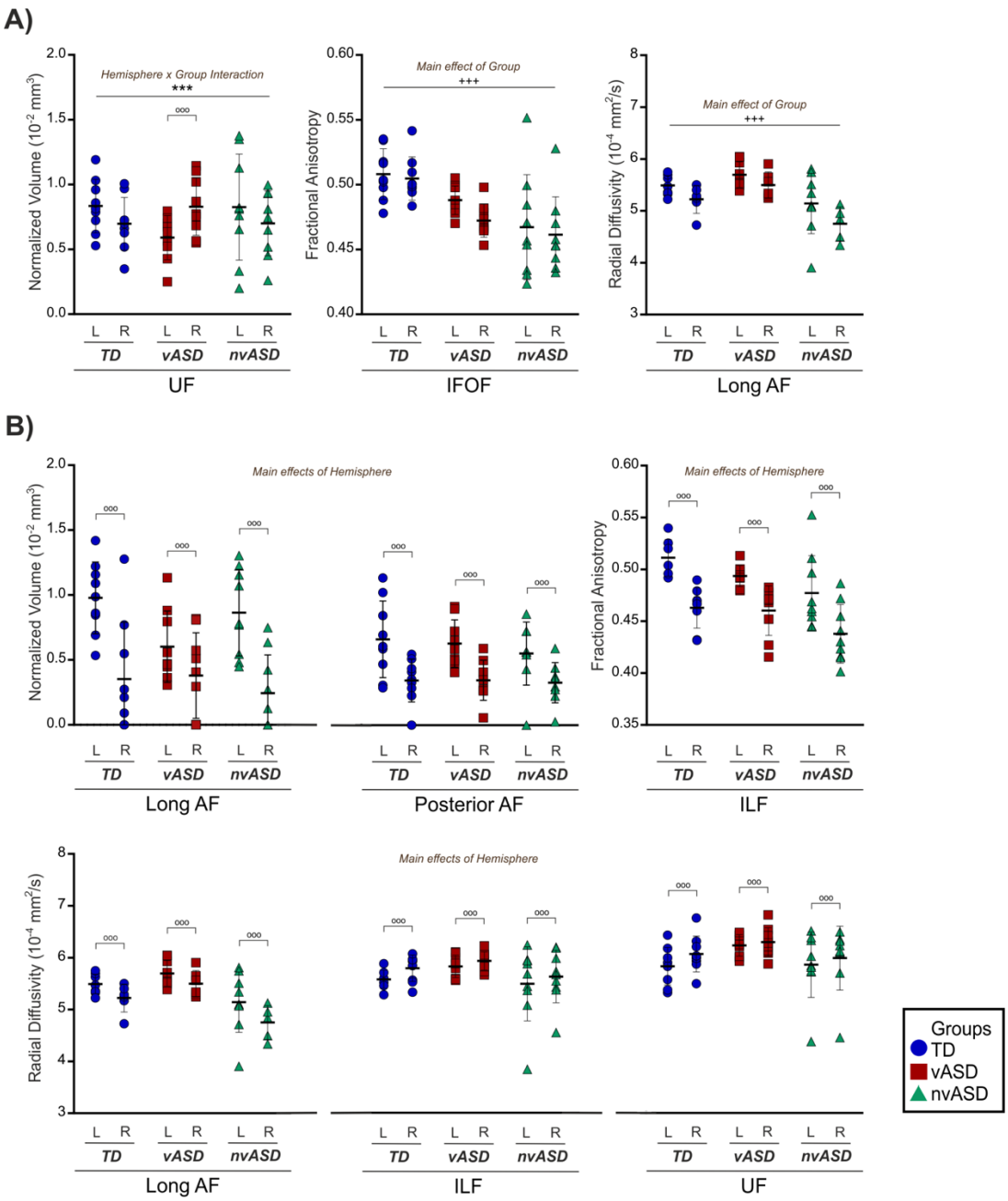

Figure 3 - Structural connectivity results: normalized volume, fractional anisotropy and radial diffusivity. Significant results of the repeated-measures ANOVA performed for the structural connectivity measures (normalized volume, FA and RD) extracted from each tract, with values for both hemispheres depicted in each group (blue circles correspond to TD participants, dark pink squares show vASD participants, and teal triangles represent nvASD participants). A) Left graph shows the distribution of normalized volume values in the UF, marking the significant *Hemisphere x Group interaction*; central graph shows the distribution of FA values in the IFOF with the *Main effect of Group* specified; right graph depicts the distribution of RD values in the Long segment of the AF, with the *Main effect of Group* specified. B) All the *Main effects of Hemisphere* found for all tracts and measures. Top row: Normalized volume values for the long segment of the AF (left) and posterior segment (center) of the AF, and FA values of the ILF (right). Bottom row: RD measures for the long segment of the AF (left), the ILF (center) and the UF (right). All results were Bonferroni corrected ($p < .005$). Abbreviations: UF = Uncinate Fasciculus; IFOF = Inferior Frontal Occipital Fasciculus; AF = Arcuate Fasciculus; ILF = Inferior Longitudinal Fasciculus; L = Left; R = Right. Figure adapted from Olivé et al., 2022.

Radial Diffusivity. A main effect of hemisphere was observed for the long segment of the AF ($F(1,14) = 9.294$, $p = 0.009$), driven by larger RD values in the left compared to the right AF. Relevantly, a main effect of group was also found in RD for the long segment of the AF ($F(2,14) = 8.813$, $p = 0.003$). Bonferroni-corrected *post hoc* comparisons showed that this effect was driven by lower RD values in the nvASD group, resulting in significant differences between vASD and nvASD groups ($F(2,14) = 9.294$, $p = 0.003$), whereas the comparisons between TD and nvASD ($F(2,14) = 9.294$, $p = 0.035$) or between TD and vASD ($F(2,14) = 9.294$, $p = 0.664$) groups did not reach significance. On the other hand, the ILF ($F(1,23) = 11.562$, $p = 0.002$) and the UF ($F(1,24) = 11.021$, $p = 0.003$) also presented significant hemisphere effects but in this case showing larger RD values on the right compared to the left hemisphere.

4. Discussion

This study aimed to investigate language-related WM structural connectivity alterations in nvASD individuals compared to matched verbal ASD (vASD) and typical development (TD) individuals. Manual DWI deterministic tractography was used for reconstruction of the main WM fiber tracks associated with language processing. We focused on individual volume, FA and RD measures as markers of white matter macro- and microstructural integrity of the tracts of interest and compared them between groups. The three main findings are, firstly, a main effect of group consisting in a reduction in FA in the IFOF in nvASD relative to the TD group; secondly, a main effect of group showing lower RD values in the long segment of the AF in nvASD compared to the vASD group; and finally, a significant interaction of hemisphere and group in the UF, which showed reduced volume in the left hemisphere when compared to the right only in the vASD group.

The reduction of FA in the IFOF in nvASD compared to TD individuals is a new finding. Although the exact involvement of the IFOF in language functions is still unclear, previous reports have demonstrated its role in reading, writing and attention (Catani & Thiebaut de Schotten, 2008; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008), but it has first and foremost been considered as a crucial pathway subserving semantic processing (Catani & Thiebaut de

Schotten, 2008; Dick et al., 2014; Fekonja et al., 2019). In line with this, several lesion and tumor studies using electric stimulation have shown the relationship between IFOF integrity and proficiency in a semantic matching task (Sierpowska et al., 2019), a verbal fluency task (Almairac et al., 2015), and the number of semantic paraphasias (H. Duffau et al., 2005; Sierpowska et al., 2019), but not for semantic learning (Ripollés et al., 2017).

To understand the IFOF's contribution in language processing, the anatomical course and terminations of the IFOF can be of great value. Recently, both DTI and anatomical post-mortem dissection studies have described the main course of the IFOF at the level of the insula and the temporal lobe (Catani & Thiebaut de Schotten, 2008; Martino, Brogna, Robles, Vergani, & Duffau, 2010), but more debate has been generated with respect to its anterior and posterior terminations. Sarubo and colleagues (2013) attempted to describe the frontal terminations of the IFOF by combining anatomical dissections and DWI. The authors proposed a division of the tract in two major components: a superficial one, terminating in the inferior frontal gyrus (IFG) and a deeper one, connecting with the middle frontal gyrus (MFG), dorso-lateral prefrontal cortex (DLPFC), the orbitofrontal cortex and the frontal pole. Similarly, Wu and colleagues (2016) used high resolution diffusion tensor tractography to identify five subcomponents of the IFOF based on its frontal terminations (which overlapped greatly with those described by Sarubo and colleagues, 2013). These results would support the idea of the IFOF as a 'multi-function' tract, with a clear involvement in language processing due to its role in conveying information to crucial language-related regions and nearby ones (IFG, MFG, DLPFC and orbitofrontal cortex). In most cases, these are associated to semantic processing functions (Binder, Desai, Graves, & Conant, 2009; Plaza, Gatignol, Cohen, Berger, & Duffau, 2008). Similarly, Martino and colleagues (2010) used post-mortem anatomical dissections to investigate and describe the posterior terminations of this tract. In this case, the authors also suggested the division of the IFOF into a superficial and a deeper component based on the posterior terminations. The former would project to the superior parietal lobe and posterior parts of the superior and middle occipital gyrus, whereas the latter would be associated with terminations in the inferior occipital gyrus and the posterior temporo-basal area. Again, the terminations of the IFOF in the associative extra-striate cortex and posterior

temporo-basal area would further support the involvement of this tract in semantic functions (Martino et al., 2010; Price, 2000; Vihla, Laine, & Salmelin, 2006).

Despite this evidence, no study until now has attempted to elucidate the role of this pathway in a disorder with a clear semantic impairment such as individuals with nvASD. In standardized settings, language comprehension measures in this group have yielded scores far below those expected by individuals' CA (Chenausky et al., 2019; DiStefano, Shih, Kaiser, Landa, & Kasari, 2016; Garrido, Carballo García, Franco, & García Retamero, 2015; Slušná et al., 2021), and caregiver reports consistently document a lack of understanding or following of complex linguistic constructions (e.g., three-step instructions) in individuals with nvASD (Skwerer, Jordan, Brukilacchio, & Tager-Flusberg, 2016). Although children with nvASD show variation in how many single words they produce, there is evidence that those words are not semantically understood as carrying referential meaning (Preissler, 2008), unlike what is seen already even in very young neurotypical infants (Marno et al., 2015). In line with this, experimental assessments using EEG have uncovered anomalous patterns of lexico-semantic neural processing in a mixed group of nonverbal and preverbal children with ASD (Cantiani et al., 2016), effectively pointing to an aberrant rather than delayed language processing, in line with the neural patterns observed here. Although lexical semantic anomalies are seen throughout ASD (Arunachalam & Luyster, 2016; Tek, Jaffery, Fein, & Naigles, 2008), these certainly do not reach the level of the essential absence of neurotypical word use in nvASD, suggesting that ventral structural alterations of the IFOF may indeed be unique to nvASD.

In this study we capitalized on manual dissection, despite it being labor-intensive and making larger samples difficult. This method was selected as it allowed a more suitable neuroanatomic approach for the research question of the study. First, manual dissections make the tract reconstruction adaptable to individual differences, which in the present case of developing brains (children and adolescents) is crucial, since most automatic dissection tools are based on adult anatomical landmarks / atlases. Second, we wanted to combine different authors' proposals for dissecting the IFOF, a complex tract for which both anterior and posterior terminations are highly controversial. Despite the multiple possible frontal terminations discussed

for this tract, all the streamlines are compacted when passing through the external/extreme capsule, so a first region of interest placed in this bottleneck should include all of the tract's fibers, as suggested by Catani and Thiebaut de Schotten (2008). However, the posterior ROI proposed by these authors is a lot more restrictive as it does not encompass some of the parietal and superior occipital terminations observed postmortem by other authors, such as Martino and colleagues (2010). Hence, we opted for a more inclusive ROI in the middle temporal gyrus, anterior to the radiation of the corpus callosum (Fekonja et al., 2019), comprising all the fibers coming from the temporal isthmus before they spread into their final cortical destination. The aim of this approach was to be as comprehensive as possible when selecting fibers, to ensure a complete and anatomically reliable characterization of the structural connectivity of this tract, which seems to be crucial for the understanding of this disorder. Nonetheless, very similar results were obtained when using the two ROIs proposed by Catani and Thiebaut de Schotten (2008) for the dissection of the IFOF as compared to the more comprehensive approach (see online resource 1).

Unlike in the case of our predictions for the ventral language pathway, our findings did not confirm our predictions based on previous literature in nvASD for structural alterations of the dorsal language pathway. These predictions were based on the study by Wan and colleagues (2012), who compared volume lateralization of the arcuate fasciculus between five completely non-verbal ASD and five TD children. Their results showed a rightward laterality (instead of the typical leftward asymmetry) in nvASD, which the authors argue could be critical for the language deficits observed in this group. However, our current results reveal lower values of RD in the long segment of the arcuate fasciculus in nvASD compared to vASD. RD can be defined as the magnitude of water diffusion perpendicular to the tract (Winklewski et al., 2018) and it has been suggested that a reduction in RD could translate into greater myelination and faster or more synchronized information transfer between brain regions (Ripollés et al., 2017). If so, this main effect of group found in the AF need not indicate an impairment in the dorsal language pathway for nvASD (as previously reported), but rather an enhanced information transfer efficiency.

The statistical and methodological limitations of our current data prevent us from a clear interpretation of this result. However, future studies could try to elucidate whether this enhanced

microstructural organization found along the long segment in nvASD individuals is actually derived from an inherent between-group tract difference, or if it is due to a compensatory mechanism to overcome the problems derived from the alterations we have observed in the ventral pathway in this same group (i.e., reduced FA along the IFOF). Nevertheless, these results make evident the need of studying the language connectome as a whole – by means of different measures across several tracts – to try to understand group differences and better characterize vASD and nvASD structural connectivity patterns in a holistic way. In principle, several factors could explain the divergence between previous and our results concerning the nvASD group: a difference in the selection of the tractography method (probabilistic vs. deterministic), in the sample size (five vs nine participants per group), or even the inclusion criteria applied (completely vs. minimally verbal ASD children). In sum, while not ruling out dorsal route involvement, our results do not support that the severe language problems observed in nvASD can be solely due to problems of sensory-motor integration related to the AF and the dorsal processing route. Instead, they point to a greater deficit involving anomalous comprehension and semantic language processing.

Although it was not the original focus of this investigation, anomalies in the ventral language route were also found here for the vASD group. Specifically, higher volume of the UF on the right compared to the left hemisphere was observed in this group, a result that converges with previous findings in both children and adults with vASD (Marco Catani et al., 2016; Y. Li et al., 2019; Samson et al., 2016). Some of this previous work proposed that the maldevelopment of the UF, a tract connecting the lateral orbitofrontal cortex and Brodmann area 10 with the anterior temporal lobe (Von Der Heide, Skipper, Klobusicky, & Olson, 2013), is a potential neural substrate for the socio-affective deficits observed in this group (Y. Li et al., 2019; Samson et al., 2016). Our vASD and nvASD individuals, however, shared a diagnosis and were selected so as to differ in language, not in socio-affective deficits. Further work is therefore required to corroborate what functions the UF supports. Given anomalies relating to the ventral route of language processing found in both ASD groups in our study, our results are consistent with a more localized ventral impact in vASD, as reflected by macrostructural alterations in a short and

restricted associative bundle such as the UF, while nvASD shows a more global effect underpinned by a microstructural anomaly in the IFOF, a massive tract crossing the entire brain ventrally. Furthermore, as neural profiles between nvASD and vASD diverge, it is possible that nvASD should not be viewed as continuous with vASD, but as a relatively separate group within the autism spectrum, with distinct structural correlates.

There are a number of limitations to this study, which we were not able to supersede during the experiment. One main limitation is the acquisition of the neuroimaging data at two different scanning sites for TD and vASD groups on one hand, and nvASD group on another. This fact also implies different scanning protocols, and while two crucial neuroimaging parameters – like voxel size or b-value – were matched, others such as coil channels or TE/TR were not. This fact may imply a bias due to the scanning protocol that cannot be dissociated from the main analyses and results. In fact, there appeared to be a slight global shift in FA and RD values for the nvASD group compared to the vASD and TD values (such as slightly lower values and higher standard deviations). These differences might be related to inherent microstructural differences in this group, and generalized scanner artifacts that resulted in this shift seem unlikely given the specificity of the patterns observed. Nevertheless, we cannot exclude the possibility that potential differences in the scanning conditions might have contributed to the observed differences. Also, the fact that dissections were performed in native space for every participant, extracting individual values from selected tracts, implies less methodological issues than voxel-based techniques performed at a group-level and implying potential registration errors. In line with this, it is important to note that very few previous neuroimaging studies have investigated nvASD participants due to the substantial difficulties of acquiring brain images of good quality in this population. If possible, future studies should try to overcome this methodological limitation by scanning at a single site or by obtaining brain data of a reduced number of subjects from both scanners (to compare and extract potential quantitative measures of control to add in the analyses). Another limitation is the reduced sample size, which, although larger than that of the key previous study (Wan et al., 2012), prevents definitive conclusions. Finally, as previously discussed, manual dissection was used for this study, but future work should try to expand the sample size and

complement the analyses with other tractography methods like TRACULA (a global probabilistic approach - Yendiki, 2011), AFQ (an automated deterministic method - Yeatman, Dougherty, Myall, Wandell, & Feldman, 2012), or tract-based spatial statistics (TBSS, to compare at group and voxel-based-like levels - Smith et al., 2006). This would help to better understand the neurobiological basis of this extreme side of the ASD spectrum, from which we know little in terms of structural neural underpinnings, despite its prevalence.

5. Conclusions

Our investigation revealed a more complex pattern of WM structural differences in nvASD than the one expected from previous findings. Unlike the previously reported disruption of the dorsal language processing route, the key finding of the present study is a reduction of FA in the IFOF in nvASD compared to TD. These results suggest the disruption of the ventral language pathway as contributing to the severe language problems exhibited at this end of the autism spectrum, in line with behavioural findings of semantic deficits in this group. Although lower RD values were found for the long segment of the AF in the nvASD group relative to the vASD group, our results clearly suggest that further investigations should not merely be centered on the articulatory-motor or dorsal route (only comprising tracts such as the AF and FAT), but that a more comprehensive investigation of the language network is needed. We also observed an increased volume in the right compared to the left UF in vASD, possibly indicating a more localized ventral processing problem in this group, which, interestingly, did not generalize to nvASD.

6. Declarations

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Conflicts of interest/Competing interests: None.

Availability of data and material: Anonymized data will be shared by request from any qualified investigator.

Authors' contributions - CRediT author statement: Guillem Olivé: Methodology, Software, Formal Analysis, Writing- Original draft preparation, Visualization. **Dominika Slušná**: Investigation, Data curation, Writing- Original draft. **Lucía Vaquero**: Validation, Formal analysis, Writing- Review & Editing, Visualization. **Jordi Muchart**: Investigation, Resources. **Antoni Rodríguez-Fornells**: Conceptualization, Writing- Review & Editing, Supervision. **Wolfram Hinzen**: Conceptualization, Resources, Writing- Review & Editing, Supervision, Project administration, Funding Acquisition.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the corresponding institutional review board (CEIC Fundació Sant Joan de Déu; PIC-99-17).

Consent to participate: Written informed consent was obtained from legal guardians of all participants.

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7. Supplementary data

Online Resource 1 – Comparison of output values (native tract volume & FA) for the two dissection methods applied to the IFOF reconstruction and ANOVA results.

Measurement & Tract	TD (n=9)	vASD (n=9)	nvASD (n=9)	ANOVA effect	F values	p (<.05)
Volume Left IFOF Catani	7.82 ± 2.38	7.56 ± 2.41	5.73 ± 2.64	**H**	5.316	0.030
				G	0.933	0.407
Volume Right IFOF Catani	8.77 ± 1.70	7.59 ± 2.78	8.13 ± 2.80	**H * G**	1.988	0.159
Volume Left IFOF Fekonja	11.62 ± 3.47	13.18 ± 4.16	10.36 ± 4.51	**H**	3.927	0.059
				G	0.059	0.943
Volume Right IFOF Fekonja	14.04 ± 3.70	11.87 ± 3.34	14.29 ± 3.68	**H * G**	3.357	0.052
FA Left IFOF Catani	0.513 ± 0.016	0.492 ± 0.013	0.477 ± 0.041	**H**	0.727	0.402
				G	6.354	0.006
FA Right IFOF Catani	0.511 ± 0.018	0.488 ± 0.011	0.472 ± 0.028	**H * G**	0.050	0.951
FA Left IFOF Fekonja	0.508 ± 0.020	0.488 ± 0.011	0.467 ± 0.040	**H**	6.925	0.015
				G	**8.062**	**0.002***
FA Right IFOF Fekonja	0.505 ± 0.017	0.472 ± 0.013	0.462 ± 0.041	**H * G**	1.461	0.252

Online Resource 1- Hemisphere (2: Left/Right) x Group (3: TD / vASD / nvASD) repeated measures ANOVAs were performed separately for each dissection method and for the volume and FA measures in the IFOF. Mean ± SD are shown for each type of dissection (Catani et al., 2008 vs. Fekonja et al., 2019) in each hemisphere (rows) organized by group (columns). Significant p-values are marked with the * sign. Abbreviations: FA = Fractional Anisotropy; TD = Typical Development; vASD = Verbal Autistic Spectrum Disorder; nvASD = Non-Verbal Autistic Spectrum Disorder; AF = Arcuate Fasciculus; FAT = Frontal Aslant Tract; IFOF=Inferior Fronto-Occipital Fasciculus; ILF = Inferior Longitudinal Fasciculus; UF = Uncinate Fasciculus; H = Hemisphere main effect; G = Group main effect; H*G = Hemisphere by Group Interaction.

Online Resource 2 - Details of ANOVA analyses for the Relative Volume measures

Measurement & Tract	TD (n=9)	vASD (n=9)	nvASD (n=9)	ANOVA effect	F values	p (<0.005)
Rel. Vol. Left Anterior Segment AF	2.5e-3 ± 2.4e-3	2.63e-3 ± 2.3e-3	2.07e-3 ± 2e-3	**H**	3.710	0.066
				G	0.442	0.648
Rel. Vol. Right Anterior Segment AF	4.1e-3 ± 2.4e-3	2.88e-3 ± 2.3e-3	2.84e-3 ± 2e-3	**H * G**	0.716	0.499
Rel. Vol. Left Long Segment AF	9.78e-3 ± 2.8e-3	6.02e-3 ± 2.8e-3	8.64e-3 ± 3.3e-3	**H**	**40.982**	**<0.001***
				G	1.021	0.375
Rel. Vol. Right Long Segment AF	3.52e-3 ± 4.4e-3	3.79e-3 ± 3.3e-3	2.45e-3 ± 2.9e-3	**H * G**	3.038	0.067
Rel. Vol. Left Posterior Segment AF	6.62e-3 ± 3e-3	6.29e-3 ± 1.8e-3	5.53e-3 ± 2.4e-3	**H**	**42.485**	**<0.001***
				G	0.320	0.729
Rel. Vol. Right Posterior Segment AF	3.44e-3 ± 1.7e-3	3.46e-3 ± 1.6e-3	3.27e-3 ± 1.6e-3	**H * G**	0.406	0.671
Rel. Vol. Left FAT	2.43e-3 ± 2.2e-3	5.07e-3 ± 2.3e-3	5.88e-3 ± 4.1e-3	**H**	0.662	0.424
				G	1.040	0.369
Rel. Vol. Right FAT	3.99e-3 ± 2.4e-3	4.55e-3 ± 3.7e-3	3.49e-3 ± 2.7e-3	**H * G**	4.207	0.027
Rel. Vol. Left IFOF	1.82e-2 ± 5.3e-3	2e-2 ± 6e-3	1.57e-2 ± 6.7e-3	**H**	4.172	0.052
				G	0.271	0.765
Rel. Vol. Right IFOF	2.24e-2 ± 6.8e-3	1.8e-2 ± 4.1e-3	2.19e-2 ± 6.3e-3	**H * G**	3.406	0.050
Rel. Vol. Left ILF	5.67e-3 ± 4.1e-3	7.72e-3 ± 3.8e-3	6.84e-3 ± 2.9e-3	**H**	0,313	0.581
				G	0.503	0.611
Rel. Vol. Right ILF	6.33e-3 ± 2.7e-3	6.8e-3 ± 3.5e-3	5.8e-3 ± 3.4e-3	**H * G**	0.492	0.617
Rel. Vol. Left UF	8.34e-3 ± 2.1e-3	5.9e-3 ± 1.7e-3	8.26e-3 ± 4.1e-3	**H**	0.041	0.842
				G	0.164	0.849
Rel. Vol. Right UF	6.97e-3 ± 2e-3	8.29e-3 ± 2.2e-3	7e-3 ± 2.5e-3	**H * G**	**9.997**	**<0.001***

Online Resource 2- Hemisphere (2: Left/Right) x Group (3: TD / vASD / nvASD) repeated measures ANOVAs were performed separately for each tract for the relative volume (Rel. Vol.) measure. Means ± SD are shown for each tract and hemisphere (rows) organized by group (columns). Significant p-values are marked with the * sign. Abbreviations: TD = Typical Developing Children; vASD = Verbal Autistic Spectrum Disorder Children; nvASD = Non-Verbal Autistic Spectrum Disorder Children; AF = Arcuate Fasciculus; FAT = Frontal Aslant Tract; IFOF=Inferior Fronto-Occipital Fasciculus; ILF = Inferior Longitudinal Fasciculus; UF = Uncinate Fasciculus; H = Hemisphere main effect; G = Group main effect; H*G = Hemisphere by Group Interaction.

Online Resource 3 – Details of ANOVA analyses for Fractional Anisotropy (FA) measures

Measurement & Tract	TD (n = 9)	vASD (n = 9)	nvASD (n = 9)	ANOVA effect	F values	p (<.05)
FA Left Anterior Segment AF	0.454 ± 0.03	0.434 ± 0.03	0.396 ± 0.05	**H**	2.956	0.105
				G	4.383	0.030
FA Right Anterior Segment AF	0.458 ± 0.02	0.448 ± 0.04	0.415 ± 0.04	**H * G**	0.353	0.708
FA Left Long Segment AF	0.483 ± 0.01	0.457 ± 0.03	0.461 ± 0.04	**H**	2.263	0.155
				G	1.785	0.204
FA Right Long Segment AF	0.493 ± 0.04	0.471 ± 0.01	0.472 ± 0.03	**H * G**	0.039	0.962
FA Left Posterior Segment AF	0.459 ± 0.03	0.456 ± 0.02	0.442 ± 0.04	**H**	0.111	0.742
				G	2.730	0.087
FA Right Posterior Segment AF	0.473 ± 0.02	0.441 ± 0.03	0.450 ± 0.02	**H * G**	1.837	0.183
FA Left FAT	0.430 ± 0.020	0.441 ± 0.021	0.426 ± 0.034	**H**	2.690	0.117
				G	0.630	0.543
FA Right FAT	0.432 ± 0.031	0.423 ± 0.034	0.410 ± 0.043	**H * G**	0.991	0.389
FA Left IFOF	0.508 ± 0.020	0.488 ± 0.011	0.467 ± 0.040	**H**	6.925	0.015
				G	**8.062**	**0.002***
FA Right IFOF	0.505 ± 0.017	0.472 ± 0.013	0.462 ± 0.041	**H * G**	1.461	0.252
FA Left ILF	0.511 ± 0.018	0.494 ± 0.010	0.477 ± 0.036	**H**	**63.097**	**<0.001***
				G	4.373	0.025
FA Right ILF	0.461 ± 0.020	0.460 ± 0.024	0.438 ± 0.028	**H * G**	0.901	0.420
FA Left UF	0.454 ± 0.030	0.423 ± 0.020	0.418 ± 0.033	**H**	8.044	0.009
				G	4.348	0.024
FA Right UF	0.433 ± 0.021	0.420 ± 0.020	0.406 ± 0.033	**H * G**	1.520	0.239

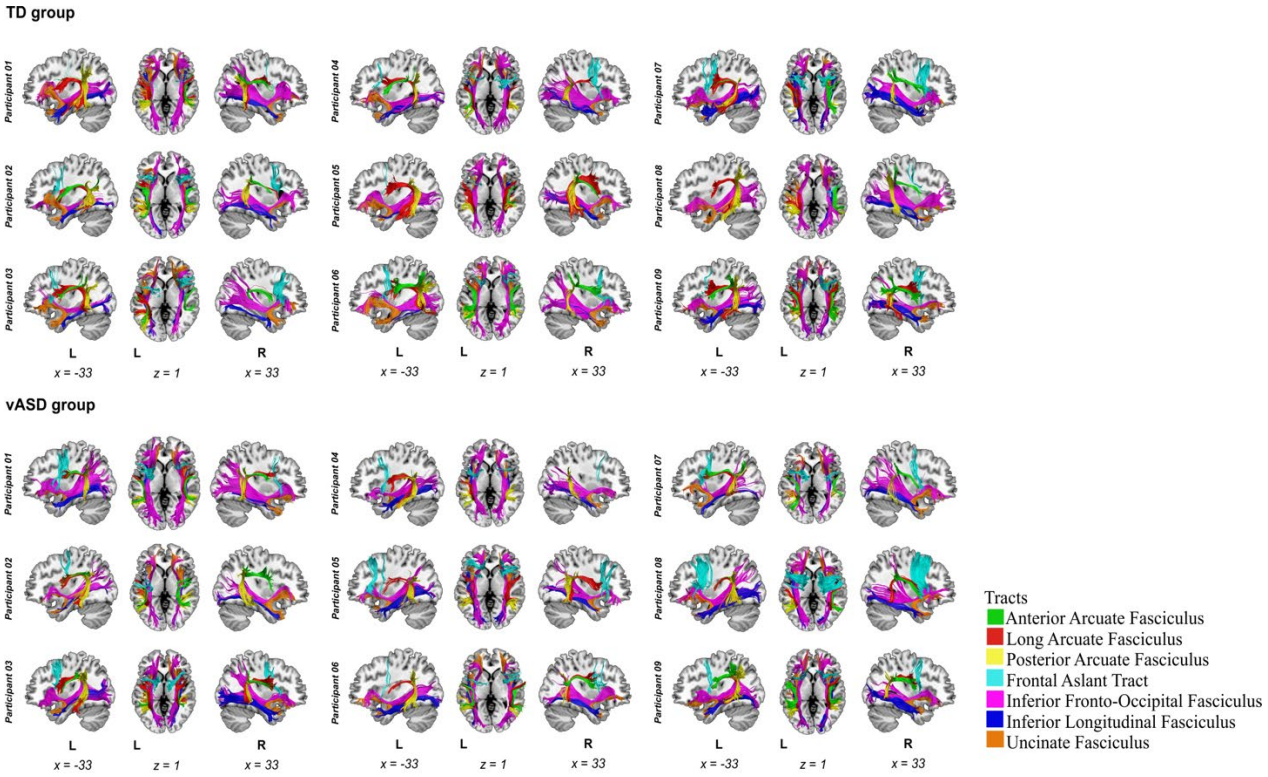
Online Resource 3- Hemisphere (2: Left/Right) x Group (3: TD / vASD / nvASD) repeated measures ANOVAs were performed separately for each tract for the fractional anisotropy measure. Mean ± SD are shown for each tract and hemisphere (rows) organized by group (columns). Significant p-values are marked with the * sign. Abbreviations: FA = Fractional Anisotropy; TD = Typical Developing Children; vASD = Verbal Autistic Spectrum Disorder Children; nvASD = Non-Verbal Autistic Spectrum Disorder Children; AF = Arcuate Fasciculus; FAT = Frontal Aslant Tract; IFOF=Inferior Fronto-Occipital Fasciculus; ILF = Inferior Longitudinal Fasciculus; UF = Uncinate Fasciculus; H = Hemisphere main effect; G = Group main effect; H*G = Hemisphere by Group Interaction.

Online Resource 4 – Details of ANOVA analyses for Radial Diffusivity (RD) measures

Measurement & Tract	TD (n=9)	vASD (n=9)	nvASD (n=9)	ANOVA effect	F values	p (<0.005)
RD Left Anterior Segment AF	5.56e-4 ± 2.1e-5	5.84e-4 ± 2.7e-5	5.67e-4 ± 4.1e-5	**H**	5.757	0.029
				G	1.493	0.254
RD Right Anterior Segment AF	5.5e-4 ± 1.6e-5	5.78e-4 ± 3.1e-5	5.49e-4 ± 4.9e-5	**H * G**	0.891	0.430
RD Left Long Segment AF	5.5e-4 ± 2.2e-5	5.67e-4 ± 2.9e-5	4.9e-4 ± 5.7e-5	**H**	**9.294**	**0.009***
				G	**8.813**	**0.003***
RD Right Long Segment AF	5.22e-4 ± 2.7e-5	5.5e-4 ± 2.5e-5	4.75e-4 ± 3.3e-5	**H * G**	0.347	0.712
RD Left Posterior Segment AF	5.59e-4 ± 2.2e-5	5.69e-4 ± 3.2e-5	5.38e-4 ± 6.7e-5	**H**	0.835	0.371
				G	1.850	0.181
RD Right Posterior Segment AF	5.42e-4 ± 2.3e-5	5.78e-4 ± 3.5e-5	5.29e-4 ± 7.2e-5	**H * G**	1.471	0.251
RD Left FAT	5.76e-4 ± 2.9e-5	5.81e-4 ± 2.8e-5	5.24e-4 ± 6.8e-5	**H**	1.954	0.178
				G	5.185	0.015
RD Right FAT	5.79e-4 ± 3.8e-5	6.02e-4 ± 3.8e-5	5.22e-4 ± 6.1e-5	**H * G**	1.635	0.220
RD Left IFOF	5.49e-4 ± 2.2e-5	5.75e-4 ± 1.8e-5	5.5e-4 ± 7.5e-5	**H**	0.756	0.393
				G	1.754	0.195
RD Right IFOF	5.5e-4 ± 2.4e-5	5.86e-4 ± 1.6e-5	5.5e-4 ± 5.5e-5	**H * G**	0.599	0.558
RD Left ILF	5.57e-4 ± 1.8e-5	5.82e-4 ± 2.2e-5	5.49e-4 ± 7.1e-5	**H**	**11.562**	**0.002***
				G	1.588	0.226
RD Right ILF	5.82e-4 ± 2.5e-5	5.93e-4 ± 1.8e-5	5.63e-4 ± 5.1e-5	**H * G**	0.757	0.480
RD Left UF	5.83e-4 ± 3.6e-5	6.23e-4 ± 2.1e-5	5.86e-4 ± 6.3e-5	**H**	**11.021**	**0.003***
				G	1.817	0.184
RD Right UF	6.07e-4 ± 3.5e-5	6.3e-4 ± 2.8e-5	5.99e-4 ± 6.2e-5	**H * G**	1.358	0.276

Online Resource 4- Hemisphere (2: Left/Right) x Group (3: TD / vASD / nvASD) repeated measures ANOVAs were performed separately for each tract for the Radial Diffusivity measure. Mean ± SD are shown for each tract and hemisphere (rows) organized by group (columns). Significant p-values are marked with the * sign. Abbreviations: RD = Radial Diffusivity; TD = Typical Developing Children; vASD = Verbal Autistic Spectrum Disorder Children; nvASD = Non-Verbal Autistic Spectrum Disorder Children; AF = Arcuate Fasciculus; FAT = Frontal Aslant Tract; IFOF=Inferior Fronto-Occipital Fasciculus; ILF = Inferior Longitudinal Fasciculus; UF = Uncinate Fasciculus; H = Hemisphere main effect; G = Group main effect; H*G = Hemisphere by Group Interaction.

Online Resource 5 – Dissections of vASD and TD participants



Online Resource 5 Manual deterministic tractography reconstructions from all participants of the TD (top) and vASD (bottom) groups. Tracts reconstructed were the three segments of the arcuate fasciculus (AF) [Green = anterior, red = long, yellow = posterior segments], Frontal Aslant tract (FAT) [Cyan], Inferior Frontal Occipital Fasciculus (IFOF) [Purple], Inferior Longitudinal Fasciculus (ILF) [Dark blue] and Uncinate Fasciculus (UF) [Orange]. Abbreviations: L, left. Montreal Neurological Institute space coordinates of the structural template slices are specified at the bottom of the image. Figure adapted from Olivé et al., 2022.

3.2 Study 2: A deficit in semantic word learning in Huntington's Disease

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A deficit in semantic word learning in Huntington's Disease

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Conflict of interests
The Authors report no conflict of interests

Abstract

Previous studies investigating language deficits in Huntington's disease (HD) have reported relatively preserved lexical and semantic systems. Nevertheless, some aspects such as semantic word learning have never been previously explored. With this aim, we compared in two different experiments early-stage HD patients with matched controls using a well-known contextual word-learning paradigm. The task required participants to infer the meaning of new words by extracting and integrating semantic cues from different sentences in a self-paced reading paradigm. The results showed that patients displayed difficulties to learn the meaning of new words from the context of the sentences (Exp. 1), which was reflected as more errors and null responses compared to controls, as well as increased reading times in conditions where meaning had to be integrated. Besides, we explored to which degree these learning differences could be attributed to working memory (WM) deficits. In Experiment 2 we ruled out this hypothesis, showing that semantic word learning was still impaired when controlling for WM load. As a control condition, we also reported that these deficits remained even though patients had no impairment to access synonyms or semantically related words of real words. These results strongly suggest a semantic learning impairment despite apparently preserved semantic processing abilities in HD patients. This research adds to growing evidence on the existence of subtle language-related impairments in HD patients, more specifically in complex language learning tasks.

Keywords: Word-learning, contextual learning, meaning, semantic integration, Huntington's disease, executive functions.

1. Introduction

Huntington's disease (HD) is a neurodegenerative disorder that leads to a progressive brain degeneration especially affecting the striatum but also involving broader cortical and subcortical regions (Gagnon, Barrette, & Macoir, 2018; Rüb et al., 2016). This striatal degeneration leads to a subsequent structural and functional disconnection between frontal and subcortical structures (Draganski et al., 2008; Leh, Ptito, Chakravarty, & Strafella, 2007; Lehéricy et al., 2004). Accordingly, early-stage HD patients already have altered cortico-subcortical connectivity (Pini et al., 2020; Poudel et al., 2014). At the clinical level, although chorea is viewed as the major symptom of HD, early on progressive cognitive and behavioral deficits are the most disabling manifestations. These deficits are usually associated with the level of atrophy of the striatum (Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005; Peinemann et al., 2005) and are present even at prodromal stages (Misiura et al., 2017). For example, subtle deficits in language as well as problems in cognitive control functions, including working memory (WM), have been previously reported (Lawrence & Sahakian, 1996; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004; Mörkl et al., 2016; Paulsen, 2011; Stoker et al., 2022; You et al., 2014). In the language domain, syntactic and morphosyntactic deficits have been reliably reported in HD patients at early and prodromal stages of the disease, sometimes also associated to dysexecutive functioning and WM impairments (De Diego-Balaguer et al., 2008; Jacquemot & Bachoud-Lévi, 2021b; Longworth, 2005; Ludlow, Connor, & Bassich, 1987; Nemeth et al., 2012; Sambin et al., 2012; Teichmann, Dupoux, Kouider, & Bachoud-Lévi, 2006; Ullman et al., 1997).

Regarding semantic processing, previous literature point to its relative integrity in HD although the evidence is inconclusive (see for positive evidence: Hodges, Salmon, & Butters, 1990; Teichmann, Dupoux, Cesaro, & Bachoud-Lévi, 2008; Teichmann et al., 2006; for negative evidence, see: Frank, McDade, & Scott, 1996; García et al., 2018; Kargieman et al., 2014; S. Smith, Butters, & Granholm, 1988). Similarly, previous deficits observed in verbal fluency do not seem to reflect core semantic problems since semantic clustering (the ability to generate successive words within a sub-category) is preserved in HD (Ho et al., 2002). However, as HD progresses, the deficits in several lexical-semantic tasks increase (e.g., performance in the Boston

Naming Test or in semantic processing tasks) (Bocanegra et al., 2015; García et al., 2018). Moreover, HD patients have difficulties with propositional language (Wallesch & Papagno, 1988) which could interfere with semantic comprehension. Importantly, a deficit in selection and inhibition, probably associated to dysexecutive functioning, could be at the source of the semantic deficits observed (Jacquemot & Bachoud-Lévi, 2021). This deficit would lead to a lexical-semantic selection impairment rather than the proper loss of semantic processing abilities. Overall, these discrepancies between studies in HD could be explained by several factors such as different stages of the disease, potential presence of dementia and the variability of methods that are used for diagnosis and evaluation of semantic deficits.

A different but related concept, albeit not explored in HD, is semantic word learning from verbal contexts. It can be conceptualized as the capacity to track and integrate the meanings of individual words across different contexts (sentence/s or paragraph/s), in order to infer the candidate meaning of a new word (Nagy, Anderson, & Herman, 1987; Nagy & Gentner, 1990; Rodriguez-Fornells et al., 2009). The study of this ability seems crucial in the case of HD given the striatum is suspected to have a role in the integration of inputs from different brain processing streams (Yin & Knowlton, 2006). The basal ganglia (including the striatum) appear as a key component in the lexical-semantic interface in ambiguous contexts, for the selection of adequate semantic-lexical items, and for the dismissal of the inadequate ones (B Crosson et al., 2003; Rodriguez-Fornells et al., 2009). Similarly, lesions in this structure appear to affect the understanding of ambiguous words, as well as the use of selective attention for the integration of semantic information (Copland, 2003), necessary for the selection of correct lexical candidates (Crosson, 1985; Wallesch & Papagno, 1988). Finally, although semantic selection occurs through the interplay between the MTG and the ventral IFG (Badre & Wagner, 2002; Gold et al., 2006; Rodd, Davis, & Johnsrude, 2005), strong striatal activation has been observed when inferring the meaning of a new word from a verbal context (Mestres-Missé et al., 2008; Mestres-Missé, Münte, & Rodriguez-Fornells, 2009; Ripollés et al., 2014; see Rodriguez-Fornells et al., 2009 for a review). Interestingly, word learning is enhanced after the administration of dopamine agonists, which modulate striatum DA-innervated pathways (Knecht et al., 2004; Ripollés et al., 2017;

Shellshear et al., 2015; Whiting, Chenery, Chalk, Darnell, & Copland, 2007). Given that the striatal degeneration observed in HD alters the dopaminergic system (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Bohnen et al., 2000; Jahanshahi et al., 2010), deficits could also be predicted in these patients in semantic word learning.

Thus, the primary aim of this investigation was to evaluate whether HD patients have difficulties in semantic word learning despite a presumably intact semantic processing. To that end, in Experiment 1 we used a previously validated paradigm known as contextual word-learning, consisting in the discovery of the meaning of a new word based on a semantic context (Mestres-Missé et al., 2008; Mestres-Missé, Münte, & Rodriguez-Fornells, 2014; Nagy et al., 1987; Nation, 2001; Rodriguez-Fornells et al., 2009). In this task, learning new words requires the inference of contextual semantic cues provided in a pair of sentences, as well as the association of this inferred concept to its corresponding new word (see Fig. 1). In this context, semantic integration is a crucial ability for a successful semantic learning, especially when trying to learn words from context (Van Berkum, Hagoort, & Brown, 1999). An advantage of this task is that it uses on-line, self-pace reading measures: sentences are presented sequentially in a one-word-at-a-time window format at a pace selected by each participant. This methodology allows to assess the reading pace of each word of the presented sentences, and therefore uses sentence reading time as an additional proxy of semantic integration effort (Mestres-Missé et al., 2014). Given the postulated critical role of the striatum in semantic processing and integration (see above), we expected that the ability of patients to derive and resolve the meaning of a new word from the context should be affected. In Experiment 2, we investigated to which extent WM deficits could affect the patients' ability to integrate the meaning across sentences, being responsible of the possible semantic word learning deficits observed in Experiment 1. With that purpose, another group of comparable HD patients (at the same stage of the disease) performed the same contextual word learning task as in Experiment 1 with a slightly modified methodology that controlled for verbal WM and cognitive load.

2. Material and Methods

2.1 Participants

We tested a total of thirty-six genetically tested Huntington's disease patients at early stage of the disease (mean TFC = 11.44, corresponding to stage I) and thirty-six healthy control participants matched in age and educational background (see Table 1), all of them recruited from the project "Biomarker HD" (NCT01590589) ethically approved from the institutional review board from Henri Mondor Hospital (Créteil, France). Half of the patients and controls were tested on Experiment 1 and half on Experiment 2. Patients from both experiments were comparable in terms of age, disease stage (all stage I) and other clinical measures ($p > .05$ for all measures), except for the Trail Making Test A (see table 1). Patients from Experiment 1 had a higher educational background [$t(33) = 3.394$, $p = .002$]. Means for all clinical and cognitive measures, as well as comparisons between experiments, can be found in table 1.

In Experiment 1, one patient did not complete the task, and thus was excluded, whereas one control was also excluded due to poor performance (equal or less than 50% correct answers). Therefore, the final sample for Experiment 1 was 17 HD patients at an early stage of the disease (stage I; see Table 1, (Shoulson, 1981); age in years: 48.5 ± 6.6; gender: 7 females; education in years: 14.5 ± 2) and 17 healthy control participants (age in years: 45.9 ± 8; gender: 8 females; education in years: 13.8 ± 1.9). The sample in Experiment 2 consisted of 18 HD patients (stage I, see Table 1; age in years: 51.9 ± 10.8; gender: 11 females; education in years: 12 ± 2.4) and 18 controls (age in years: 48.1 ± 8.9; gender: 9 females; education in years: 12.8 ± 2.3). The control group participating in Experiment 2 was also matched in age and educational background to the patient group. All participants gave informed consent.

	Experiment 1	Experiment 2*	Normal published range	Test result	p value
TFC	11.2 (1.1)	11.7 (1)	13	-1.416	0.166
UHDRS motor score	29.5 (13.9)	25.4 (15.3) (n = 16)	0	0.712	0.482
CAG-repeats	44.6 (2.2)	44.1 (1.8)	10-29	0.690	0.495
MDRS	124.8 (13.9)	130.7 (9.8) (n = 15)	≥ 136	-1.368	0.182
Stroop interference	23 (14.4)	30.9 (14.7)	≥ 35	-1.572	0.126
Verbal fluency 2 min	26.7 (22.8)	38.4 (17.9)	18	-1.656	0.108
Symbol Digit Code	27.9 (16.5)	29 (11.1)	≥ 37	-0.231	0.818
HVLT A	18.9 (6.5)	21.1 (6.1) (n = 15)	26.3 (3.6)	-0.971	0.339
HVLT B	6 (3.6)	7 (3) (n = 15)	9.7 (1.6)	-0.851	0.401
HVLT C	10.2 (2)	10.9 (1.3) (n = 15)	11.7 (0.6)	-1.060	0.298
TMT-A	105 (69.6)	64.1 (25.4) (n = 16)	31	**2.267**	**0.034**
TMT-B†	20.6 (6.9)	21.1 (6.4) (n = 16)	-	0.996	0.327

Table 1. **Neurological and neuropsychological data of HD patients**.
Data shows the group means for each measure, with the standard deviation between brackets. Between-group differences were explored using an independent samples t-test. Statistically significant group differences are marked in bold letters. *N is provided when data is not available for all the participants. †Because most patients did not connect the 25 circles within the time limit (240s), the score reported here is the number of circles connected. Abbreviations: TFC = Total Functional Capacity; UHDRS = Unified Huntington's Disease Rating Scale; MDRS = Mattis Dementia Rating Scale; HVLT = Hopkins Verbal Learning Test, A: Immediate recall, B: delayed recall, C: recognition; TMT = Trail Making Test.

2.2 Neurological and neuropsychological Evaluation

The motor and cognitive subscales of the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996) were used as measures of HD progression for each patient. The assessment of executive functions was performed using the following tests: the Trail Making Test parts A and B (TMT; Tombaugh, 2004), and the symbol digit code test (Wechsler, 1981) to measure sequencing and processing speed; the Stroop test (Golden, 1978) to study inhibitory control; and a verbal letter fluency task (Butters, Wolfe, Granholm, & Martone, 1986) to assess selection. The Stroop interference task is a widely used measure of selective attention that requires interference

resolution, response inhibition and response selection (MacLeod & MacDonald, 2000), whereas the symbol digit code task requires speed processing, set-switching, problem solving and attention (Galvin, Tolea, Moore, & Chrisphonte, 2020). Both tasks rely on selective attention, which is a relevant function in semantic processing (Van Petten, 2014), learning and memory (Chun & Turk-Browne, 2007). These tests are the most frequently used tests to assess executive dysfunction in HD and systematically detecting deficits in this disease (Beglinger et al., 2005; O'Rourke et al., 2011; J. S. Paulsen et al., 2001). In addition, the general cognitive assessment included the Mattis dementia rating scale (MDRS; Mattis, 1976) and the Hopkins Verbal Learning Test (HVLT; Rieu, Bachoud-Lévi, Laurent, Jurion, & Dalla Barba, 2006) for measures of immediate and delayed episodic memory. The results of the different tests are summarized in Table 1.

2.3 Experimental material

The experimental software EXPE6 (Pallier, Dupoux, & Jeannin, 1997) was used for the administration of the task, and it was run on a Pentium-based PC. The learning task reported in this study is a French adaptation of a task used in previous studies with healthy populations (Mestres-Missé et al., 2008) that allows successful word-meaning learning. Participants were required to read triplets of sentences, each triplet ending in a new word (a non-existent word that maintained the phonotactic rules of French). The participant's objective in the semantic integration task was to infer the new word meaning from the context provided in each triplet of sentences.

The experiment featured three conditions (see examples below with English translation in brackets): meaningful condition (M+), in which a new word meaning could be inferred from the three sentences of the triplet; non-meaningful condition (M-), in which a new word meaning could not be extracted; and (R), in which real words were used.

1. Meaningful condition (M+):

Marie ne supporte pas l'odeur des *giales* (Marie cannot stand the smell of *giales*)

Paul ira s'acheter un paquet de *giales* (Paul went to buy a pack of *giales*)

Le soir je fume mes deux dernières *giales* (In the evening I smoke my last two *giales*)

2. Non-meaningful condition (M-):

Hier ils sont venus installer le nouveau *corsit* (Yesterday they came to install the new *corsit*)

Paul doit rentrer pour aller nourrir ses *corsits* (Paul has to go back to feed his *corsits*)

Depuis samedi Céline porte une alliance au *corsit* (Since Saturday Céline wears a wedding *corsit*)

3. Real-word condition (R):

Elle aime décorer la maison avec des *bougies* (She likes to decorate the house with *candles*)

Attention ne vous brûlez pas avec la *bougie* (Be careful not to burn yourself with the *candle*)

Pour masquer l'odeur on allumera une *bougie* (To mask the smell we will light a *candle*)

The meaning of the new words corresponded to 36 medium frequency French nouns with a mean frequency of 67.25 per million. For each original noun, three sentences were constructed with an increasing degree of contextual constraint (i.e. cloze probability, the probability of a word completing a particular sentence). To obtain the cloze probabilities for the new sentences, we prepared three different questionnaires. We split the triplets of sentences to be used in the experiment and presented one of these sentences in each questionnaire. Each questionnaire was administered to 8 different healthy participants that did not participate in the experiment. All the sentences were missing the last word, and participants were asked to complete each sentence with the word they thought fitted best. This methodology allowed us to extract the cloze probability from each individual sentence. An additional fourth questionnaire, featuring the three sentences of each triplet together, was also administered to calculate the cloze probability of each triplet. Mean cloze probability was: first sentence (low constraint) 8.93% (SD = 14.18), second sentence (medium constraint) 45.33% (SD = 20.91), and third sentence (high constraint) 88.25% (SD = 11.51). The probability of meaning identification across the three sentences was 98.3% (SD = 3.03).

In order to minimize possible differences due to phrase construction, sentences were systematically rotated between the three experimental conditions creating three lists of 36 sets of three sentences (12 M+, 12 M- and 12 R) counterbalanced across participants. Each list was

further divided into 4 blocks of 9 sets of three sentences (3 M+ triplets, 3 M- triplets and 3 R triplets). The M- condition was built by mixing the first, second and third sentence of different triplets resulting in a different combination of three sentences, incongruent across the triplet.

2.4 Experimental procedure

Two different experiments were conducted in this study, which used the same experimental material but had different objectives and slightly different designs. A schematic of the experimental design of both experiments is depicted in Figure 1.

The main experiment of this study was Experiment 1. In this Experiment, participants were presented with triplets of sentences ending in a new word. A non-cumulative moving-window methodology (Mitchell, 1984) was used to ensure that participants carefully read each word: sentences were presented sequentially in a one-word-at-a-time window format. This methodology allows to detect at which point of the sentence difficulties in meaning integration arise. Initially each sentence appeared on the screen with all characters replaced by dashes. Participants pressed the space bar to reveal the first word, and each subsequent button press revealed the next word and replaced the previous word with dashes. Reading latencies for each word were recorded as the time interval between successive button presses. At the end of the last word of the sentence, the screen was replaced by the next sentence in the same manner until the three sentences of a triplet were read. After the presentation of the three sentences, a prompt was shown requiring participants to report the meaning of the new word, or a synonym/semantically related word in the case of real-words (*meaning discovery test* from now on). There was no time limit to respond. If participants did not know the answer or were not able to extract it, they had to press the enter key to move on to the next trial. This option could apply to the M- condition, in which meaning discovery was not possible. It also applied to M+ triplets for which meaning discovery was possible, but participants did not succeed, in which case the answer was computed as an omission.

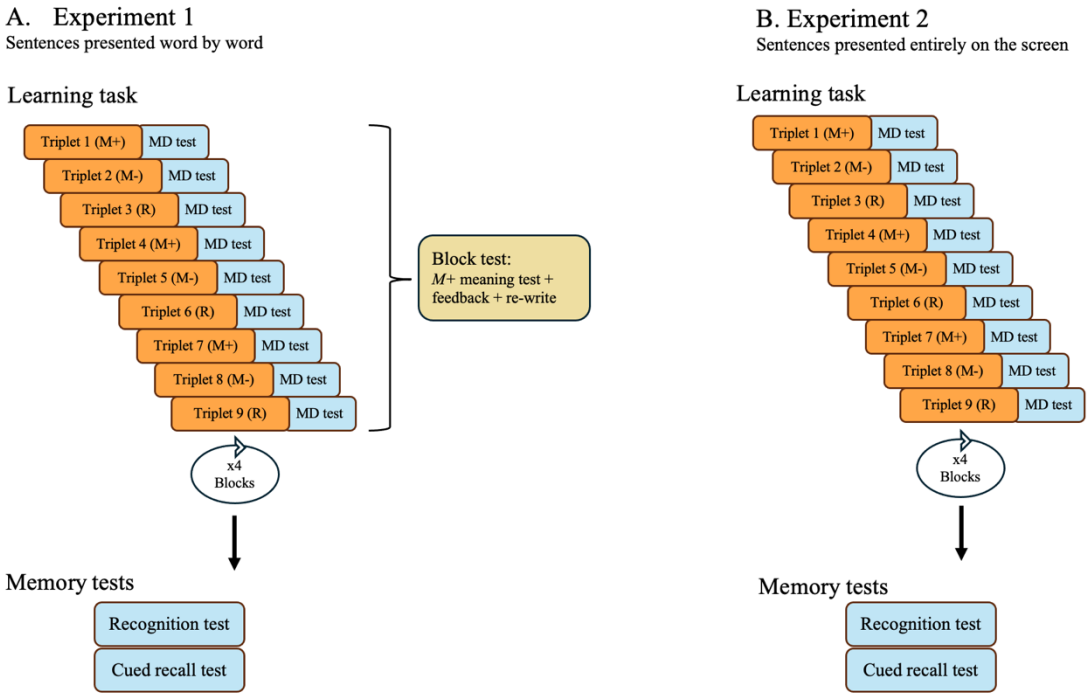

Figure 1 – Design of the contextual word-learning task.
Schematic overview of the contextual learning task administered in the two experiments of the study. Warm colors indicate learning tests while cold colors show memory tests. **A.** Schematic of the task as administered in Experiment 1, in which the presentation of the triplets of sentences was done sequentially (word by word). During the learning task, triplets of sentences were grouped in four blocks of nine (three M+ triplets, three M- and three R), after which a block test was administered. After the completion of the four blocks, two memory tests (recognition and cues recall tests) were administered. **B.** Schematic of the task as administered in Experiment 2, in which the sentences were presented entirely on screen. In this experiment, no block test was administered at the completion of the learning task block, moving directly to the next block. The rest of the task was identical to the one from Experiment 1. Abbreviations: M+: meaningful condition; M-: non-meaningful condition; R: real-word triplet; MD: meaning discovery test.

The task was presented in blocks of 9 triplets that included 3 M+, 3 M- and 3 R triplets. After the presentation of each block (9 triplets), new word meaning inference for the M+ words was tested (*block test*). New words from the M+ condition were presented alongside the prompt-text 'the word means', and participants were required to type the meaning of the new word. In order to ensure that they correctly encoded the correct meaning, after typing their answers and/or after pressing the key button, feedback was provided with the text: 'new word' means '*meaning*'. Subsequently, participants were asked to rewrite again what the new word meant following the same procedure as before. The goal of this phase was to reinforce meaning association to the new words and therefore was not analyzed. Once the block test for block 1 was completed, participants then repeated the same procedure for block 2 and so on, until the four blocks of the experiment were learnt and tested in the same manner.

Immediately after the completion of the entire semantic integration task, participants performed a *memory test*, in which the memory for the learnt words was tested. This test consisted of two subparts, assessing two different processes. The first subpart was a *recognition test* in the form of a paper and pencil questionnaire with 48 new words: 12 M+ and 12 M- from the preceding semantic integration task, and 24 fillers. Fillers were novel words that were never presented before. Participants were asked to indicate which new words they recognized from the previously presented sentences by circling them. This measure evaluated the memory of word forms. The second subpart was a cued recall test. Alongside each new word presented in the questionnaire, the first letter of their meaning was presented as a cue. However, only for the M+ words this letter corresponded to the actual meaning, as only for this condition participants were able to infer a correct meaning, whereas in the M- words and fillers the letter presented did not hold any meaning or possible association. Known as phonetic cueing, this methodology was also used in previous new-word learning studies in order to evaluate learning in patients with cognitive deficits facilitating recall (Tort-Merino et al., 2017; Tuomiranta et al., 2014). In this cued recall test, participants were asked to try to report the meaning associated with each new word. This measure allowed to test the strength of the association between the new word and the corresponding meaning extracted from the sentences. One patient did not complete this test; hence, from the sample analyses in the self-paced reading task, data from 16 patients and from the 17 controls were included in this analysis.

On the other hand, Experiment 2 was conceived as a control to evaluate the impact of WM on the results obtained from experiment 1. Therefore, the experimental design was slightly modified compared to the one described in experiment 1. The main modification was that the moving window methodology was no longer used for the sentence presentations. In this case, after the presentation of an asterisk on the screen for 1000 ms, the first sentence of a triplet was presented all at once. Participants were required to press the space bar once they had read the whole sentence. The space bar press revealed the second sentence of the triplet. It appeared under the first sentence, which remained on the screen. At the following space bar press, the third sentence

was presented under the previous two sentences that remained on the screen. After reading the third sentence, participants had to press the space bar again, which led to the meaning discovery test for that triplet. Given that this experiment was a used as a control of the previous one, the learning reinforcement provided by the block test was not conducted. Deleting the block test substantially simplified the task and reduced the administration time of the experiment. Right after the completion of the four learning blocks, participants performed the same memory tests as described in Experiment 1. Two patients did not complete this test; hence, data from 16 patients and 18 controls were included in this analysis.

2.5 Outcome measures

All statistical analyses were conducted using the IBM SPSS software (v25.0). Several measures were used as indicators of performance for the two experiments. The principal measure of semantic word learning was the accuracy of the meaning discovery test for M+ new words. This measure was computed by dividing the number of correctly inferred meanings by the total number of M+ words. For the incorrectly reported M+ meanings, the percentage of errors (number of incorrect meanings provided divided by total M+ new words) and omissions (number of words for which no meaning was provided divided by total M+ new words) were also calculated. These percentages were compared between groups in each experiment.

Some control measures were also computed from the meaning discovery test. On the one hand, we wanted to control that participants were not focusing only on the last sentence of the triplet to give an answer instead of integrating the meaning of the three sentences. To do so, we calculated the number of times patients and controls reported a meaning congruent only with the last sentence in the M- condition. Necessarily, this analysis was performed considering only the M- condition. This is because in the other two conditions (M+ and R), the three sentences were congruent and the contextual cues from all the sentences led to the same meaning. Therefore, there was no way of knowing whether the response provided was guided by the information from the three sentences or just the last one. On the other hand, we also extracted the number of correct

synonyms (or semantically related word) reported by participants for the real-word condition to control for semantic processing ability.

Additionally, the reading times of the semantic word learning task were also extracted. In Experiment 1, in which the words from each sentence were presented sequentially, each word's reading time was computed as the time between the button press revealing that word and the button press revealing the next word. According to previous research using the same task and the same sentence presentation methodology (Mestres-Missé et al., 2008), no differences in the reading times are observed between conditions (M+, M- and R) until the penultimate word of the sentence, although the maximum differences are observed only for the last word. After checking that this was also the case in both the group of patients and controls, only the last word (the new word) from each sentence was compared between groups in Experiment 1. In order to directly compare Experiments 1 and 2 with the same measures, the sentence reading time in Experiment 1 was also calculated as the sum of the reading times of each word forming the sentence. This metric was calculated and compared between Experiments and to explore how reading patterns differ depending on the methodology used for the sentence presentation.

In Experiment 2, reading time was simply computed as the time between the button press revealing that sentence and the button press revealing the next sentence. In the reading time analysis, for the M+ condition, only sentences for which participants correctly inferred the new word meaning were included. In all conditions and for each participant, reading times 2 standard deviations above or below their mean were also excluded from the analysis.

Finally, several measures were obtained from the cued recall test. The percentage of correctly recognized new words was obtained by dividing the number of recognized new words by the total number of new words presented (M+ and M- words). Additionally, the percentage of correctly recalled meanings was computed by dividing the number of correctly recalled M+ new words by the total number of M+ new words. The recognition analysis was performed for all new words presented. However, the percentage of correctly recalled meanings was only performed for the M+ words since they were the only ones that held any meaning (and therefore the only ones for which a meaning recall was possible).

3. Results

3.1 Experiment 1

3.1.1 Semantic word learning task

The mean percentages for correctly inferred new words, errors and omissions, were calculated for each subject and compared between groups (patients and controls) separately by using an independent samples t-test. HD patients identified fewer correct meanings of the new words than controls [patients: 64.7% ± 26.11% vs. controls: 89.7% ± 10%; $t(20.60) = -3.69$, $p = .001$] (see Figure 2). The incorrect responses of the patients were constituted of both a greater proportion of errors [patients: 20.6% ± 16.4% vs. controls: 9.3% ± 8.8%; $t(24.45) = 2.49$, $p = .020$] and omissions [patients: 14.7% ± 23.5% vs. controls: 1% ± 2.8%; $t(16.44) = 2.39$, $p = .029$] than controls.

Notwithstanding, patients were as good as controls in reporting a synonym (or semantically related word) for the real-word condition [patients: 96.57% ± 5.9 % vs. controls: 96.35% ± 5.2%; $p > 1$]. We also controlled if patients were focusing more on the last sentence compared to controls. Pairwise comparisons revealed no significant differences between groups in the number of times they reported a meaning congruent only with the last sentence in the M-condition [patients: 13.24% ± 15.9% vs. controls: 18.14% ± 20.9%; $t < 1$].

The reading time analysis was performed in both experiments using a 3 x 2 mixed ANOVA for each condition including the repeated-measures factor Learning (1st, 2nd, 3rd sentence) and the between-subjects factor Group (Patient, Control). Subsequent Bonferroni corrected pairwise comparisons between the groups were also performed. In Experiment 1, for these analyses, a comparable amount of sentences deviating more than 2 SD from the mean was excluded in all conditions for both groups for (patients: 5.3% vs. controls: 5.9 % of the responses; $t(32) = -1.07$, $p = .293$).

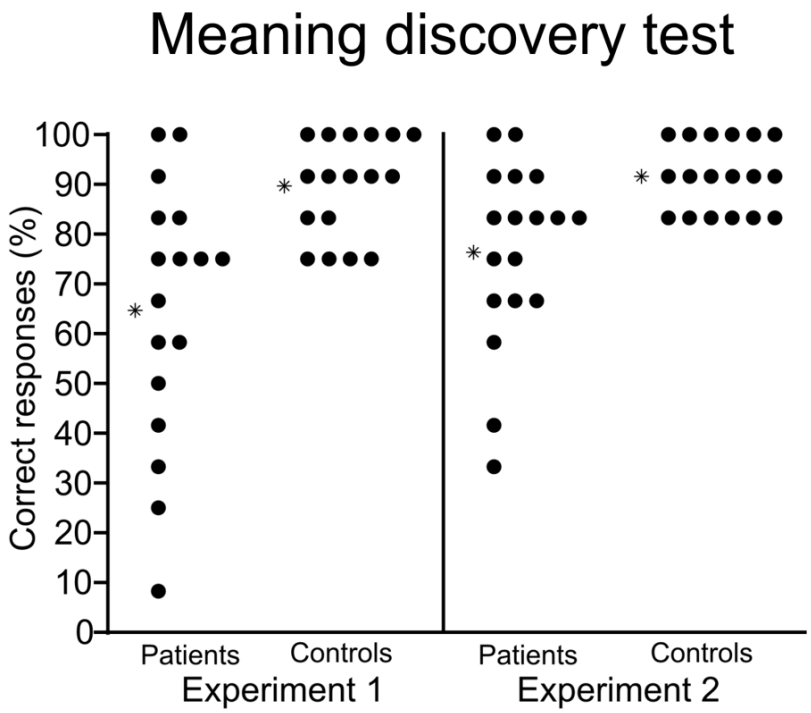

Figure 2. Mean percentage of correctly learnt meanings per group. Group means are depicted with an asterisk. Dots represent each participant's performance. Bars represent standard error of the mean.

For the real-word sentences (see Figure 3 top), both patients and controls decreased their reading time of the last word (real word) as sentences proceeded [1st vs. 2nd R sentence ($p = .037$); 1st vs. 3rd ($p < .001$); 2nd vs 3rd ($p = .21$)] (see Table 2). In contrast, both new word conditions revealed a clear interaction between Learning and Group (Table 2), reflecting the different pattern of reading times across groups. In the M+ condition, patients showed significantly increased reading times than controls on the last word of the 3rd sentence ($t(32) = 2.40$, $p = .022$). That is, while controls showed a reduction in reading times in the new word of the 3rd sentence for the condition where meaning could be inferred, patients showed an increased reading time. Interestingly, in the M- condition where meaning could not be inferred (incongruence across sentences), both groups showed an increase in reading times of the new word in the 3rd sentence (3rd vs 2nd M- sentence, $p = .017$). However, while controls showed the expected increase in reading times of the new word across all sentences, patients showed a different pattern, with faster reading times than controls on the last word of the 2nd M- sentence ($t(32) = -2.64$, $p = .013$).

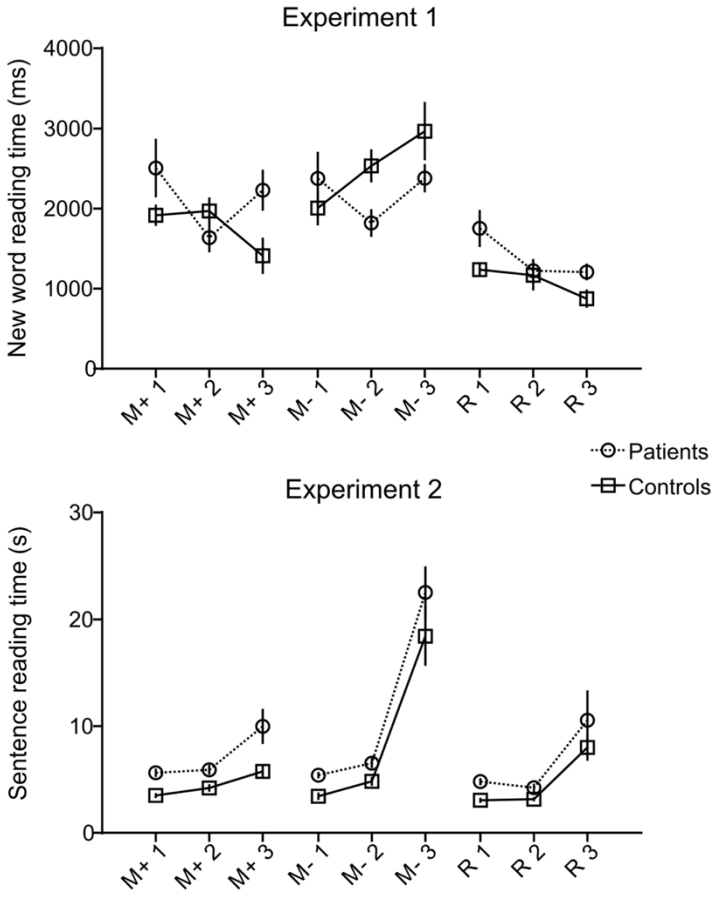

Figure 3. Reading times for the last word (Experiment 1) and sentence (Experiment 2) for each condition for patients and controls. Bars represent standard error of the mean.

3.1.2 Recall test

Two-sample t-test analyses on the data of the recall test showed no significant differences between patients and controls in the total amount of recognized new words [patients: 21.88% ± 16% vs. controls: 30.15% ± 12.44%; t(31) = 1.633, p = .113]. From this total, for patients vs. controls respectively, 57.5% ± 25.26% vs. 66.21% ± 14.08% corresponded to M+ new words [t(31) = 4.543, p < .001]; 27.55% ± 16.62% vs. 28.68% ± 11.9% corresponded to M- new words [t(31) = 1.309, p = .200]; and 14.95% ± 17.03% vs. 5.12% ± 7.7% corresponded to false recognition of fillers [t(20.78) = -1.602, p = .132]. In contrast, differences were found for the meaning recall part, as the correct M+ meaning was reported significantly more often for controls than patients [patients: 14.06% ± 22.6% vs. controls: 63.41% ± 25%; (t(23) = -4.74, p < .001].

3.1.3 Semantic word learning and neuropsychological assessment scores

In order to explore the relationship between semantic word learning and the other neuropsychological measures associated to verbal learning and executive control, Pearson correlations were carried out. Using a False Discovery Rate correction (FDR; $p < 0.01$) for adjusting multiple comparisons, we observed that semantic learning in HD patients was significantly associated with executive function tests (verbal fluency, Stroop and Symbol Digit Code) and verbal learning, assessing recognition, immediate and delayed verbal memory (subtests of the HVLT) (see Table 3). Overall, a strong relationship between semantic word learning and executive control was observed that might also be associated to the cognitive load imposed in the first experiment, where participants had to read the sentence and keep it in memory during the presentation of the second sentence. In experiment 2, we tried to minimize cognitive load and WM demands, presenting both sentences at the same time.

	Experiment 1			Experiment 2		
	df	F value	η_p^2	df	F value	η_p^2
M+						
Learning	2, 64	3.55*	.10	1.129, 38.403	15.39***	.31
Group	1, 32	ns	.06	1, 34	10.45**	.24
LxG	2, 64	6.18**	.16	2, 68	ns	.06
M-						
Learning	1.549, 49.577	3.45*	.10	1.029, 34.976	71.11***	.68
Group	1, 32	ns	.04	1, 34	3.83†	.10
LxG	2, 64	3.80*	.11	2, 68	ns	.01
R						
Learning	2, 64	10.84***	.25	1.022, 34.732	13.99***	.29
Group	1, 32	ns	.08	1, 34	ns	.07
LxG	2, 64	ns	.08	2, 68	ns	.01

Table 2. 2-way (Learning: 1st, 2nd, 3rd; Group: patient, control) mixed ANOVAs for each sentence for experiment 1 and experiment 2. Note: Learning (L); Group (G). When sphericity was violated, the Greenhouse-Geisser correction was used. †p = .06 – .05; *p < .05; **p < .01; ***p < .001; ns: not significant.

3.2 Experiment 2

3.2.1 Semantic word learning task

In Experiment 2, when controlling for WM load, patients showed again an impairment to correctly identify the meanings of the new words compared to controls [patients: 76.4% ± 18.4% vs. controls: 91.7% ± 7%; t(21.845) = -3.299, p = .003] (see Figure 2). Patients made more omissions [patients: 9.7% ± 9.6% vs controls: 1.8% ± 4.6%; t(34) = 3.144, p = .003] and tended to produce more errors than controls [patients: 13.9% ± 15.1% vs. controls: 6.5% ± 6.7%; t(23.486) = 1.898, p = .070]. Similarly to the previous experiment, patients reported a synonym or semantically related word for the real-words from the R condition comparably to controls [patients: 90.28% ± 16% vs. controls: 95.37% ± 7.7%; t(24.461) = -1.219, p = .235]. For the M- condition, patients and controls showed no significant differences in the number of meanings reported corresponding only to the last sentence of the triplet [patients: 10.7% ± 9.4% vs. controls: 10.7% ± 8%; p > .1)]. In the analyses of reading times for the real-word sentences (see Fig. 2 bottom), patients and controls showed no significant reading time differences. However, in contrast with the previous experiment, both groups read 3rd R sentences slower than the two first sentences [3rd vs 1st R sentence (p = .003) and 3rd vs 2nd (p = .001)]. For M+ sentences, both groups showed longer reading times in the 3rd sentence compared to the other two sentences [3rd vs. 1st M+ sentence (p < .001) and 3rd vs. 2nd (p = .004)] (see Table 2 and Fig. 2 bottom). For the M- condition, both groups showed an increase in reading times as sentences proceeded (Bonferroni corrected pairwise comparisons, all p < .001).

In order to discern whether the differences found between experiments in the pattern of reading times were a consequence of the WM load reduction in the 2nd Experiment, we aggregated reading times of all words in Experiment 1 to compare the same measures across experiments. A mixed ANOVA was then performed with sentence (1st, 2nd, 3rd sentence) and condition (M+, M-, R) as within-subject factors, and Experiment (Experiment 1, Experiment 2) and Group (Controls, Patients) as the between-subject factors. No statistically significant

interaction was found between group and experiment (supplementary material, Figure S1). This reveals that the semantic learning deficits observed in HD cannot be accounted for by the WM load of Experiment 1. In addition, this result indicate that the difficulties are only observable in the reading times when analyzing the last word of the sentence.

3.2.2 Recall test

Patients and controls did not differ in the total amount of recognized new words [patients: 20.57% ± 6.3% vs. controls: 21.06% ± 10.4%; $t < 1$] and in any of the conditions in the recall test after the learning phase: from this total, in patients and controls respectively, 38.28% ± 19.2% vs. 38.41% ± 20.8% ($t < 1$) corresponded to M+ new words, 36.03% ± 16.2% vs. 45.12% ± 17.5% ($t(32) = -1.56$, $p = .127$) corresponded to M- new words, and 25.69% ± 20.2% vs 16.47% ± 14.8% ($t(32) = 1.53$, $p = .136$) corresponded to false recognition of fillers. Moreover, the groups did not differ in the amount of meanings reported [patients: 3.64% ± 6.3% vs controls: 13.54% ± 26.6% ($t(32) = -1.453$, $p = .156$)]. From those, the correct M+ meanings [patients: 40% ± 54.8% vs. controls: 20% ± 42.2% ($p > .1$)] and incorrect meanings provided [patients: 20% ± 44.7% vs controls: 14% ± 32.7% ($p > .1$)] were also comparable between groups. The groups did not differ either in the proportion of meanings reported for a M- new word or for a filler [patients: 40% ± 54.8% vs. controls: 66% ± 47.2% ($t > 1$)].

3.2.3 Semantic word learning and neuropsychological assessment scores

In contrast with Experiment 1, semantic word learning in HD patients was not significantly correlated with any of the neuropsychological measures after FDR-correction for multiple comparisons. Overall, the present pattern of correlations reinforces the idea that in Experiment 2 we were able to minimize cognitive and executive demands compared to the first version of the experiment.

	Semantic word learning Experiment 1	Semantic word learning Experiment 2
Stroop interference	**.633**	.415
Verbal fluency 2 min	**.594**	.169
Symbol Digit Code	**.628**	.435
HVLT A-immediate recall	**.582**	.373
HVLT delayed recall	**.584**	.349
HVLT C-recognition	**.633**	-.079
TMT-A	**-.613**	-.365
TMT-B	**.581**	.455

Table 3. Pearson correlations between percentage of correct responses in the semantic integration task and neuropsychological assessment scores. Correlations significant after FDR-correction ($p < .01$) are marked in bold.

3.3 Comparison between experiments: Recall test

Two-way ANOVAs (Experiment: 1 vs. 2; Group: patient vs. control) were performed for each of the dependent variables extracted from the recall test to study the effect of experiment. The analyses revealed that in Experiment 1 both groups significantly recognized more M+ new words ($F(1,63) = 24.03$, $p < .001$, $\eta p2 = .28$) than in Experiment 2. Similarly, in Experiment 1 they both reported more meanings in general ($F(1,63) = 16.07$, $p < .001$, $\eta p2 = .20$), and less meanings were falsely reported for M- and R new words ($F(1,63) = 11.92$, $p = .001$, $\eta p2 = .25$) than in Experiment 2. Conversely, in Experiment 1 compared to Experiment 2, significantly less M- new words ($F(1,63) = 10.01$, $p = .002$, $\eta p2 = .14$) and fillers ($F(1,63) = 7.87$, $p = .007$, $\eta p2 = .11$) were recognized.

4. Discussion

The main aim of this study was to assess the integrity of semantic word learning ability in individuals with HD. To this end, we adapted a previously used contextual learning task (Mestres-Missé et al., 2014; Ripollés et al., 2014) that required individuals to track and integrate the

meanings of different sentences in order to properly infer the meaning of the new word. Both the reading times of the triplets and the learning success of the new words could be used as indicators of the state of semantic word learning ability, which were compared between HD and control groups. Our findings across experiments and controlling for cognitive load revealed that HD patients at early stages of the disease have difficulties in extracting word meanings from contexts compared to control participants.

In the current task, reading the first sentence of each triplet provided information that allowed participants to select a number of lexical candidates that could fit the new word meaning. In the case of the M+ condition, reading the second and third sentences provided additional semantic information. If the information from the different sentences was properly integrated, it allowed to narrow down the primed semantic space and select the most fitting lexical candidate for the new word. According to previous studies, the striatum appears to have a critical role in this process of semantic selection by conflict monitoring and selecting the best fitting final candidate (Crosson et al., 2003; Rodriguez-Fornells et al., 2009). This is consistent with the notion that the privileged position of basal ganglia not only gives it a coordinating function between language streams and other cognitive functions, but it is also fundamental in learning situations or when there is ambiguity in language (Copland, McMahon, Silburn, & de Zubicaray, 2009; De Diego-Balaguer et al., 2008; Friederici & Kotz, 2003; Wahl et al., 2008). Previous neuroimaging research applying the same paradigm as the one used here but in healthy population has identified the striatum as an active region in the extraction of the meaning of new words embedded in verbal contexts (Mestres-Missé et al., 2008, 2009; Ripollés et al., 2014). In addition, the striatum displayed a role in the retrieval of information based on contextual cues (Scimeca & Badre, 2012). On the grounds of the evidence discussed above, the semantic learning deficits observed in HD may stem from their characteristic striatal degeneration, but also from the subsequent structural and functional disconnection between frontal and subcortical structures. Previous studies have shown the involvement of frontal regions in learning (Seger, 2005), in the processing of pre-selected lexical items (Crosson et al., 2003), retrieval of semantic knowledge (Ullman, 2006) and,

more importantly, in the contextual acquisition of words (Mestres-Missé et al., 2008; Mestres-Missé, Rodriguez-Fornells, & Münte, 2010).

This hypothesis goes in line with the differences found between groups regarding sentence reading times. In Experiment 1, in both new word conditions (M+ and M-), controls showed the reading time pattern previously observed (Mestres-Missé et al., 2014), which is: reduced reading times for the 3rd sentence in meaningful conditions, and gradually increasing reading times for sentences in non-meaningful conditions (see Figure 3). However, even when patients successfully inferred the meaning of the new word, reading times for the last word of the 3rd M+ sentence were not reduced and were not different from the last M- sentence. Moreover, faster reading times in 2nd M- sentences suggests that patients may not detect the incongruence between the 1st and 2nd M- sentences. An alternative explanation for this result would be that HD patients prioritized the 1st and 3rd sentences, paying less attention to the 2nd one, to reduce memory demands. However, if it was indeed a strategy adopted by participants, it would have made more sense they prioritized the second and third sentence and devoted less attention to the first sentence instead, given that it was the least informative out of the three. Altogether, the results show an impairment of HD patients in semantic word learning, which is manifested as a lower proportion of correctly learnt meanings, as well as the different reading time patterns when compared to controls.

Aside from the discussed role of the striatum in semantic integration, previous reports have related this structure with other verbal-related functions such as executive functions, including verbal WM or verbal attention. These processes have been related with selection mechanisms that have a determinant role in language processing (Jacquemot & Bachoud-Lévi, 2021). Therefore, it would be plausible to attribute the group differences found in HD patients to alterations in executive functions. In this sense, the effect of cognitive load and WM in semantic learning was controlled for in Experiment 2. In this second experiment, the cognitive and WM load was considerably reduced as participants could see the entire sentence on the screen during each trial. Indeed, no significant correlations between neuropsychological scores in these domains and word

learning appeared in the second experiment compared to the first one (see Table 3). However, the results presented above indicate that despite cognitive and executive functions can affect performance in the extraction of meaning from context, patients still presented semantic word learning deficits when this cognitive and WM load was reduced. Specifically, patients showed an impairment to correctly infer the meanings of the new words compared to controls.

This deficit beyond executive control is reinforced by the results from reading times. In experiment 2, the patterns of reading times across sentences are strikingly similar for HD and controls (see Figure 3), as both groups read the 3rd sentences slower than the two first sentences in the R and M+ conditions, whereas they showed an increase in reading times as sentences unfolded in the M- condition. Notice that for M+ and R conditions, the three sentences of the triplet were congruent with each other. Thus, reading times for the 3rd sentence of M+ and R conditions may not only reflect the processing of that sentence, but also its integration with the previous two sentences (which remained on the screen), as well as the successful inference of a meaning in the M+ condition. On the contrary, M- stimuli were incongruent across the three sentences. This was reflected in the gradual increase of reading times from the first to the third sentence, and in the 3rd M- sentence showing significantly longer reading times compared to the 3rd sentence of the other two congruent conditions in the two groups. The results obtained here go in line with previous reports, showing that readers spend longer reading times and show larger number of eye-movement regressions when trying to infer the meaning of new words in less informative or less familiar contexts (Chaffin, Morris, & Seely, 2001), or in cases of higher semantic ambiguity (Duffy, Morris, & Rayner, 1988). Similarly, a previous fMRI study used the same paradigm as the one administered here to investigate the neural bases of word learning in healthy controls. The results showed an increased activation in the anterior cingulate cortex for the M- condition, signaling the presence of conflict across potential semantic pre-activated candidates and a larger effort devoted to this condition (which parallels the longer reading times in the last sentence of this condition) (Mestres-Missé et al., 2008). In our study, although both groups showed a similar pattern of sentence processing, HD patients were slower overall in reading times only in the conditions where new word meanings had to be extracted (M+, M-).

This result suggests an increased effort in accessing meanings in these patients, which may have consequences for semantic integration abilities.

Although no statistically significant relationship was observed in Exp. 2 between executive functioning and verbal learning and word-learning, it is important to mention that the correlations observed follow the same trends as in Experiment 1, in which all of them were strongly correlated with word-learning performances. Therefore, results from both Experiments point to the important role of executive functioning and verbal learning in these tasks, corroborating previous ideas on the important contribution of domain general mechanisms in the early stages of word learning (De Diego-Balaguer et al., 2008; Rodriguez-Fornells et al., 2009). Most probably, in the executive domain, inhibition, flexibility, selection or selective attention processes might be relevant to integrate and properly learn the meaning of the new word from the semantic features activated.

On the other hand, one could think that differences between groups in the semantic word learning task could be caused by a semantic processing deficit in patients. As reviewed in the introduction, previous literature examining semantic processing in HD was inconclusive (García et al., 2018; Kargieman et al., 2014; Teichmann et al., 2008, 2006), with some studies suggesting that the striatal and thalamic degeneration observed HD could have an impact on semantic processing ability (García et al., 2018; Wahl et al., 2008). Therefore, its influence on semantic word learning could not be excluded beforehand and needed to be tested. That is why in the current experiment we added the R condition. In that condition, the triplet of sentences presented did not end in a new word but in a real word instead, for which participants had to generate a synonym or a semantically related word. This condition allowed us to assess the semantic processing ability, since the correct generation of a synonym required the participant to have preserved semantic access, selection and retrieval of a fitting lexical candidate (Mollo et al., 2016). Although the semantic activation required for this task might not be highly demanding, and therefore would allow a slight semantic deficit to go unnoticed, it allows to detect significant deficits in semantic

processing. Nevertheless, our results showed no differences in the R condition, as patients and controls were comparable in reporting synonyms. This implies that the differences between groups found in the meaning discovery tests for the M+ and M- conditions cannot be attributed to impaired semantic processing, since group differences were not observable in the condition where meaning integration was not necessary. However, a note of caution should be pointed out since R condition does not allow us to completely rule out the presence of mild semantic deficits in patients. Moreover, the process of integrating contextual cues and semantic associations with relevant discourse information and inhibiting irrelevant information is built on interactions between syntactic and semantic processes (Kuperberg, Caplan, Sitnikova, Eddy, & Holcomb, 2006). Therefore, some mild unnoticed semantic deficits combined with previously described syntactic deficits in HD (Giavazzi et al., 2018; Hinzen et al., 2018) may exacerbate the word learning impairments observed here. It may also induce problems in comprehension tasks involving multiple sentences beyond individual word meanings (Kuperberg et al., 2006; Zwaan & Radvansky, 1998).

Finally, the data from the memory tests provided information about the interaction between semantic and episodic memory during word learning processes in the current cohort (Laine & Salmelin, 2010; Peñaloza et al., 2022; Rodriguez-Fornells et al., 2009). The recognition test required participants to recognize which of the items in a list were previously presented in the learning phase. It mainly focused on the memory of word forms and is usually more associated with the dorsal language pathway (Dick et al., 2014; López-Barroso et al., 2013). Both groups were comparable in new word recognition in both experiments and in both the M+ and M- conditions, pointing to a relatively spared episodic memory system. Then, participants had to recall the meaning of the new words learned, in the condition where this was possible (M+). This cued recall test tapped into the strength of the association between the learnt new words and their meanings, a process usually more related to the ventral language stream (Ripollés et al., 2017, 2014). Here is where deficits were observed in Experiment 1 only: control participants recalled more correct M+ meanings and reported less incorrect M+ meanings than patients. This result

suggests the interleaved tests and feedback provided in Experiment 1 benefited the encoding and recalling of meanings of M+ new words in controls but not in patients. This result could point to a distinct effect of repeated recall on patients compared to controls. Recognition and recall deficits have previously been reported in HD, although some controversies can also be found in the literature (El Haj, Caillaud, Verny, Fasotti, & Allain, 2016; Solomon et al., 2007; see Montoya et al., 2006 for a metanalysis). Our results in the recall test and in the HVLT neuropsychological evaluation are consistent with the notion of a relatively preserved recognition but difficulties for recall in HD.

We acknowledge that even if the block test was conceived as a way to reinforce the previously learnt words, some learning was still possible at this point. Therefore, we cannot exclude the possibility that this second learning instance was differentially exploited by the two groups, benefiting more the controls and explaining the better results from this group in the recall test of experiment 1. However, it might simply show a better association between the new words and its learnt referents from the control group.

In conclusion, this study points to a semantic learning deficit present in early-stage HD patients as seen by an increased difficulty in extracting the meaning of new words from contextual cues and increased reading times in conditions where meaning had to be integrated. In tasks such as the one used here, where the activated meaning from the contextual cues needs to be integrated, we observed difficulties that are not explained by WM or cognitive or executive load limitations, in line with previous work by Sambin and colleagues (2012). Also, our real word condition and the results from previous reports of semantic tasks in patients at different stages of the disease indicate that this deficit is not due to a global semantic deficit per se, but rather to a specific problem with integration (Jacquemot & Bachoud-Lévi, 2021). Overall, our findings complement previous studies in HD that only reported syntactic deficits with spared lexical retrieval. The results presented in this study are highly relevant given the scarcity of previous research focusing on more subtle specific language disabilities in HD. Future research could expand the results

presented in this study by applying neuroimaging techniques to study the specific contributions of different striatum sub-regions, and other subcortical structures such as the thalamus in the process of semantic word learning. The presented results might help gain some understanding on the linguistic impairments of HD patients, ultimately having an impact on their management and well-being.

5. Supplementary material

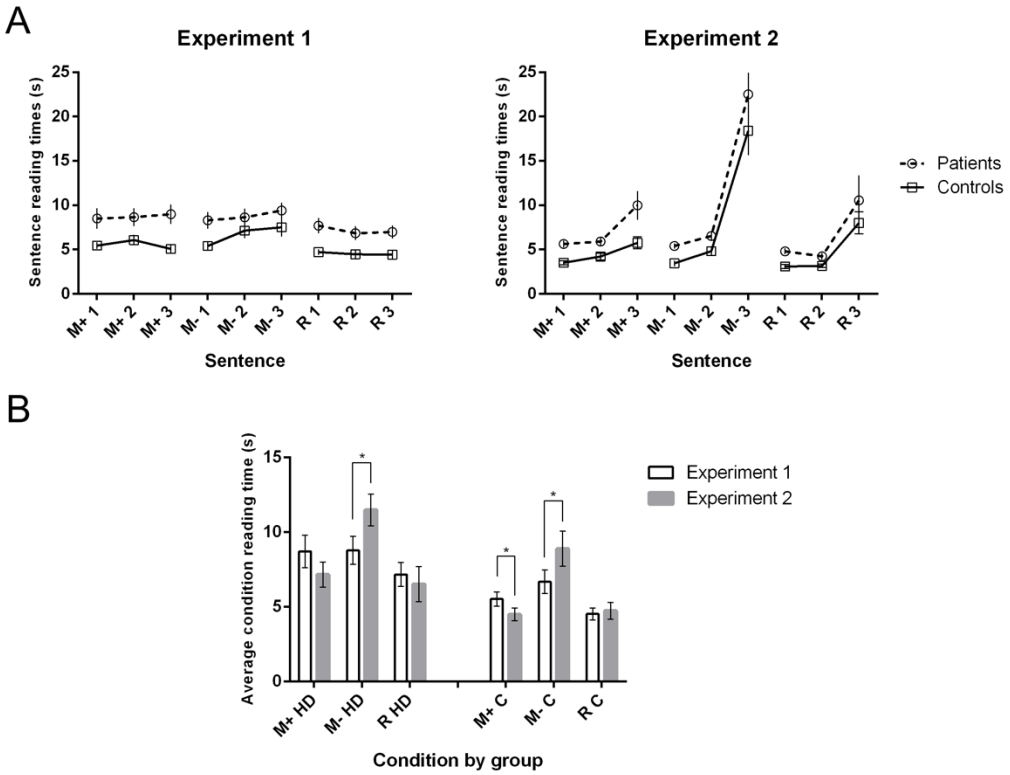

Figure S1 – Comparison of whole sentence reading times between Experiments. **A** Whole sentence reading times for Experiment 1 (left) and Experiment 2 (right). **B** Comparison between Experiments of the mean reading time of the three sentences from for each condition (M+, M-, R) independently for each group. Asterisks signal significant differences between experiments for each condition at a significance level of $p < 0.05$. Abbreviations: 1 = first sentence, 2 = second sentence; 3 = third sentence; M+ = congruent condition; M- = incongruent condition, R = real-word condition.

3.3 Study 3: Impaired semantic word learning in primary progressive aphasia

This work is under review in the journal Cortex, and would corresponds to:

Olivé, G., Cardona, G., Porto, M.F., Gerloff, A., Marqués-Kiderle, S., Filella-Mercè, J., Sala., I., Sánchez-Saudinós, M.B., Armas, P., Peñaloza, C., Grasso, S.M., Bejanin, A., Alcolea, D., Illan-Gala, I., Fortea, J., Lleó, A., Vaquero, L., Rodríguez-Fornells, A., Santos-Santos, MA. Impaired semantic word learning in primary progressive aphasia.

Impaired semantic word learning in primary progressive aphasia

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Abstract

The neuropsychological and linguistic impairments in individuals with primary progressive aphasia (PPA) have been largely studied. However, the integrity of word learning ability in different PPA variants remains unexplored, despite its prominent role in language therapy. In this study, we investigated the novel word learning ability of 20 individuals with PPA (non-fluent variant: nfvPPA n = 11; logopenic variant: lvPPA n = 9) as compared to 23 neurotypical controls (NC). Specifically, we used a contextual word learning task that required participants to discover the meaning of 48 new words across several sentences via inference from verbal contexts. We further conducted an exploratory analysis in a subsample of 8 nfvPPA, 5 lvPPA and 17 NCs using manual deterministic tractography to investigate the relationships between the language-related white matter tracts' integrity and learning accuracy. The results revealed overall impaired word learning ability in individuals with PPA when compared to NCs, and worse learning performance for individuals with lvPPA relative to nfvPPA. The tractography analyses revealed that radial diffusivity values from both dorsal and ventral language tracts were associated with learning accuracy. Our findings provide novel insights that increase our understanding of language learning impairment in individuals with PPA.

1. Introduction

Primary Progressive Aphasia (PPA) is a neurodegenerative clinical syndrome mainly characterized by prominent speech and/or language impairment, without other cognitive domains being initially affected (M. M. Mesulam, 1982, 2001). The observed communication impairment is caused by a selective neurodegeneration of left hemisphere language regions. The current diagnostic classification framework differentiates between three main subtypes of PPA: non-fluent/agrammatic (nfvPPA), logopenic (lvPPA) and semantic (svPPA) variants (Gorno-Tempini et al., 2011; Rohrer et al., 2013). NfvPPA is characterized by motor and syntactic deficits and is usually associated with frontal neurodegeneration, especially in the inferior frontal gyrus (IFG) and premotor regions. LvPPA is defined by repetition and word finding impairments, and degeneration usually affects the posterior superior (STG) and middle temporal gyri (MTG), as well as the posterior inferior parietal lobe (IPL). Finally, individuals with svPPA present naming and single word comprehension deficits and a marked anterior temporal lobe degeneration. Despite these differences, the categorization of individual cases into specific PPA subtypes is often complex especially in the early stages of the disease (Volkmer et al., 2020), and particularly between nfvPPA and lvPPA, given their partial feature overlap (Hinkley et al., 2023). Importantly, speech and language therapy is the most recurrent approach in clinical practice to ameliorate the described deficits given its proven efficacy to improve this condition and the lack of any curative treatment (see Grasso et al., 2023; Wauters et al., 2023 for reviews). However, great variability of treatment effects is observed among people with PPA (PwPPA), even across individuals with the same clinical profile (Tippett, Hillis, & Tsapkini, 2015). This underscores the need for continued efforts in the characterization of PPA subtypes and the identification of relevant factors determining individual treatment outcomes and prognosis beyond language processing ability and neural damage.

The ability to learn novel word-referent mappings (hereafter: word learning WL ability) may provide relevant insights in this context. A thorough assessment of WL abilities is crucial in PPA, as many current therapies for anomia are based on the individual's ability to engage language

learning and re-learning processes. These processes aim to restore language function and regaining access to known lexical semantics or phonology that become inconsistently available (Basso et al., 2001; Martin, Fink, Renvall, & Laine, 2006; Middleton, Schuchard, & Rawson, 2020). Indeed, previous proposals point to WL as a way to enhance therapy outcomes (Coran, Rodriguez-Fornells, Ramos-Escobar, Laine, & Martin, 2020) via stimulation of neuroplasticity processes (Kelly & Armstrong, 2009). Thus, assessing WL in this population could improve predictions of re-learning therapy response and facilitate the translation of these findings into improved treatments. Besides, the assessment of WL ability in PPA could enhance our understanding of the disease and the underlying differences between variants, thus helping to improve diagnostic categorization and serving as an early index of learning impairment in dementia as previously seen in Alzheimer's disease (Tort-Merino et al., 2017) and language recovery in post-stroke aphasia (PSA) (Tuomiranta et al., 2014).

The investigation of language learning mechanisms in adults is rather complex, as this ability relies on the coordinated activity of multiple systems, including language processing streams, episodic memory, cognitive control, and domain-general learning systems (Peñaloza et al., 2022; Rodriguez-Fornells et al., 2009). Numerous studies accrued during the past two decades have been conducted to better understand the neural underpinnings of WL in the neurotypical brain (Davis & Gaskell, 2009; Li, Legault, & Litcofsky, 2014; Rodriguez-Fornells et al., 2009; Tagarelli, Shattuck, Turkeltaub, & Ullman, 2019). It has been observed that novel WL is supported by a segregated cerebral network composed of several brain regions including the STG, MTG, IPL, the prefrontal cortex and the middle temporal lobe (Mestres-Missé et al., 2014, 2010; Ripollés et al., 2017, 2014).

Despite the extensive research of this ability in the neurotypical adult population, WL preservation in the presence of brain damage or neurodegeneration is still only partially understood (see Peñaloza et al., 2022 for a review). Research conducted with individuals with PSA shows significant interindividual variability in WL and overall lower capacity when

compared to neurotypical controls (Coran et al., 2020; Dignam et al., 2016). However, some individuals with PSA show relative preservation of explicit associative word learning with both familiar and new words (Coran et al., 2020; Navarrete-Orejudo et al., 2023; Tuomiranta et al., 2011, 2012), as well as implicit 98re learning (Peñaloza et al., 2015, 2017). Regarding its neuroanatomical basis, the integrity of both dorsal (AF) and ventral (ILF) tracts has been previously linked to success in WL tasks in PSA (Coran et al., 2020; Tuomiranta et al., 2014), corroborating the important role of these white-matter pathways in supporting language learning, as previously observed in neurotypical adults (López-Barroso et al., 2013; Ripollés et al., 2017).

Far less research has been conducted to examine the functionality of WL ability in PwPPA. Existing studies have mainly focused on the ability of people with svPPA to relearn previously known words, considering that word retrieval difficulties and the progressive loss of semantic knowledge are core features of this variant. Overall, studies have shown limited but successful relearning in this population, although there is a frequent deterioration of relearned words without continued training, as well as limited generalization effects (see Shebani & Patterson, 2024 for a review). On the other hand, the evaluation of novel language learning ability is practically non-existent in nfvPPA and lvPPA, with the exception of a single study demonstrating reduced artificial grammar learning in nfvPPA compared to controls (Cope et al., 2017). Consequently, no study has evaluated the ability to acquire new word meanings, or semantic WL ability, in these two variants. It is likely that the preservation of semantic processing in these PPA variants has been assumed to guarantee semantic WL learning, although this has not previously been formally tested.

The main aim of this study was to assess whether semantic WL ability is preserved in nfvPPA and lvPPA. Based on the literature and the atrophy pattern in lvPPA, which overlaps with important brain regions for semantic WL (such as the STG, IPL and MTG, Mestres-Missé et al., 2010; Ripollés et al., 2017), we expected this group to show reduced accuracy on measures of WL outcomes compared to nfvPPA, who do not usually show maximal regional atrophy in these

regions (Tee & Gorno-Tempini, 2019). Similarly, we expected both PPA groups should show an impairment compared to neurotypical individuals. This hypothesis is supported by previous studies that reported various degrees of impairment in both variants in cognitive domains related to language learning, such as working and episodic memory (Eikelboom et al., 2018), phonological processing (Mesulam et al., 2009) or subtle semantic mapping impairments (Thompson et al., 2012) as compared with NCs. We also explored potential distinctive traits in WL for acquiring different classes of new words (nouns vs. verbs) given that this is still an open question generating a growing interest in the field (Alyahya et al., 2020; Hoffman, Jones, & Lambon Ralph, 2013; Mestres-Missé et al., 2010; Shapiro et al., 2005; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). To test our hypotheses, we investigated semantic WL using a well-known contextual word learning (CTXL) task previously used in young neurotypical adults (Mestres-Missé et al., 2014). In this task, learning new words mainly requires the inference of contextual semantic cues provided in a pair of sentences, as well as the association between the inferred concept and its corresponding novel word form (see Figure 1). Furthermore, we used manual DTI tractography reconstructions to evaluate the extent to which CTXL depended on the microstructural integrity of underlying language-related white-matter tracts reflecting both dorsal and ventral language routes (Olivé et al., 2023). For this exploratory aim, we expected to find an association between learning accuracy and both the integrity of ventral tracts related to meaning processing –as reported in previous studies testing CTXL (Mestres-Missé et al., 2008, 2009; Ripollés et al., 2014)– and dorsal tracts given that learning also entails the acquisition of new phonological word forms (López-Barroso et al., 2013).

2. Materials and Methods

2.1 Participants

Participants were 24 PwPPA (11 nfvPPA, 13 lvPPA) and 23 Neurotypical Older Controls (NOC), recruited from a local hospital in Barcelona, Spain. All participants spoke Spanish with native fluency. Individuals were diagnosed with PPA by a specialized neurologist by clinical

examination, reviewing behavioral data according to current diagnostic criteria for nfvPPA, svPPA, and lvPPA (Gorno-Tempini et al., 2011), and inspecting their respective structural MRI images. The following exclusion criteria were employed: (i) previous neurological/psychiatric disorders excluding PPA; (ii) previous traumatic brain injury; (iii) uncorrected auditory and/or visual deficits. Four lvPPA individuals were excluded from the study as they were unable to understand the instructions to complete the WL task and failed to correctly answer the training sentences of the task. Therefore, the final sample consisted of 20 PwPPA (11 nfvPPA: 5 female, mean age = 72 ± 9.78; 9 lvPPA: 2 female, mean age = 76 ± 6.17) and 23 NOC (14 female, mean age = 65 ± 10.35). All participants provided their written informed consent to undergo study procedures in accordance with the Declaration of Helsinki. An additional group of 32 undergraduate psychology students, hereafter neurotypical younger controls or NYC (27 females, mean age = 20.5 ± 1.98) were recruited to validate the experimental task and ensure it would capture enough individual variability in learning performance. None of the participants in the NYC group met any of the exclusion criteria. All NYC were recruited at the University of Barcelona (Barcelona, Spain), gave their informed written consent, and were paid or received course credit for their participation. The demographic data for each group alongside their performance on neuropsychological testing are summarized in Table 1.

2.2 General Cognitive and Language Assessment

Individuals from both PPA groups and the NOC group underwent neuropsychological evaluation as previously described (Alcolea et al., 2019). This evaluation was administered in Spanish and included: the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), the Clinical Dementia Rating (CDR) (Morris & Louis, 1994), the Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 2005), the letter fluency and category fluency tests (Pena-Casanova et al., 2009), the Free and Cued Selective Reminding Test (FCSRT; Grau-Guinea et al., 2021), the forward and backward digit span (Wechsler, 1981), and the Trail Making Test parts A and B (TMT; Tombaugh, 2004). Descriptive statistics for these scores can be found in Table 1.

	NOC (22)	nfvPPA (11)	lvPPA (9)	Test result	p value
Demographic information					
Sex (male/female)	8 / 14	5 / 6	6 / 3	2.386	0.306
Handedness (R/L/A)	20 / 0 / 2	11 / 0 / 0	6 / 2 / 1	9.100	0.059
Native Language (Spanish monolingual / Bilingual with native level of Spanish)	19 / 3	7 / 3	6 / 3	1.946	0.378
Age (Years)	66.81 (54.74 -73.01)	74 (67.46 – 77.7)	75.81 (71.73 – 82.5)	9.888	**0.007**[a]
Years of Education (Years)	17 (12 – 20)	12 (11 – 14)	14 (10.75 – 17)	4.575	0.102
Span between sessions (Days)	42 (17.50 – 83)	114 (13 – 157)	145 (7.5 – 155)	0.312	0.856
Span between MRI scan and the first evaluation session (Days)	152 (134 – 361)	118.5 (59.5 – 163.75)	123.5 (65.5 – 166.5)	4.908	**0.014**[b]
General Cognitive Measures					
MMSE	29 (28 – 30)	27 (26 – 29)	26 (24.5 – 28.5)	12.892	**0.002**[c]
CDR	-	0.5 (0.5 – 0.5)	0.5 (0.5 – 0.5)	50	0.340
TPO (days)	-	1288 (1006 – 1899)	1464 (1146.75 – 3194.5)	40	0.291
General Cognitive and Language Assessment					
BNT	55 (50 – 57)	48 (39 – 54)	37 (23.25 – 46.25)	20.262	**< 0.001**[d]
Letter fluency	16 (14 – 17)	7 (3.5 – 12.25)	10 (4.75 – 11.5)	19.240	**< 0.001**[c]
Category fluency	18 (16 – 24)	11 (7 – 14.5)	9.5 (7.25 – 10.25)	24.664	**< 0.001**[c]
FCSRT-IFR	26 (23 – 30)	15 (9.75 – 21.5)	11 (5 – 16)	15.739	**< 0.001**[c]
FCSRT-ICR	46 (44 – 47)	39 (29.25 – 44)	23.5 (8.75 – 34.75)	22.527	**< 0.001**[d]
FCSRT-DFR	12 (10 – 13)	6.5 (4 – 9)	4.5 (0 – 6.25)	19.969	**< 0.001**[c]
FCSRT-DCR	16 (15 – 16)	13.5 (10 – 15.25)	10.5 (0.75 – 12.5)	19.410	**< 0.001**[c]
Forward digit span	5 (5 – 6)	4 (4 – 5)	5 (4 – 6)	5.711	0.058
Backward digit span	4 (4 – 5)	3 (2.75 – 4)	3.5 (3 – 4.25)	9.754	**0.008**[b]
TMT-A	37 (31 – 55)	74 (57.5 – 94.5)	57 (43.75 – 102.75)	14.720	**0.001**[c]
TMT-B	84 (73 – 112)	287.5 (245.5 – 700)	188 (143 – 421.5)	25.960	**<0.001**[c]

Table 1 – Demographical and neuropsychological profiles across study groups.
Data are medians and the first and third quartile between brackets (Q1 – Q3). Between-group differences were explored using $\chi 2$ tests for sex, handedness, and bilingualism; Mann-Whiney tests for Clinical Dementia Rating (CDR) test and the time post-onset of the symptoms (TPO); and One-way ANOVA for the rest of measures. Statistically significant group differences are marked in bold letters. Post-hoc tests were performed for the variables where a between-groups significant difference was found. Results were represented as follows: [a] Differences between NOC and lvPPA groups; [b] Differences between NOC and nfvPPA groups; [c] Differences between NOC and both nfvPPA and lvPPA groups; [d] Differences between NOC and both nfvPPA and lvPPA groups and also between nfvPPA and lvPPA groups. Abbreviations: NOC = Neurotypical Older Controls; nfvPPA = Non-fluent variant of Primary Progressive Aphasia; lvPPA = logopenic variant of Primary Progressive Aphasia; L = Left; R = Right; A = Ambidextrous; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; TPO = Time Post Onset; BNT = Boston Naming Test; FCSRT-IFR= Free and Cued Selective Reminding Test – Immediate Free Recall; FCSRT-ICR= Immediate Cued Recall; FCSRT-DFR = Delayed Free Recall; FCSRT-DCR = Delayed Cued Recall; TMT = Trail Making Test.

2.3 Word learning task

2.3.1 General design

The experimental WL task is an adaptation from a paradigm used in previous studies (Mestres-Missé et al., 2014, 2010; Ripollés et al., 2017). Participants were required to read 48 duplets of sentences that always ended in a new unfamiliar word (a pseudoword that stood for a real word, either a noun or a verb). For each duplet, participants could infer the meaning of the new word from the semantic contextual cues provided in the sentences. An example of a sentence duplet is as follows:

> "Por su cumpleaños, Juan le regaló un *BETO*" (For his birthday, Juan got him a *BETO*).
>
> "Para 102re n moto es obligatorio ponerse *BETO*" (To ride a motorcycle, it is mandatory to wear a *BETO*).
>
> Hidden Word meaning: Casco (Helmet).

Hence, the participant's objectives in this task were to: (i) extract the new word meaning from the context provided in each duplet of sentences; (ii) learn the novel word form, and (iii) map the association between the new word's form and the hidden meaning.

The task included two learning conditions (nouns and verbs) and it was administered in two sessions conducted on different days (mean lapse between sessions = 77.5 ± 73.3 days, no significant difference between PwPPA and NOC groups in session spans: F= .571, p= .570). Both learning conditions had the same task structure. In the noun condition session, participants had to learn the meaning of 24 new words that stood for nouns whereas in the verb condition session they had to learn 24 new words that corresponded to verbs. Therefore, participants were required to learn 48 new words in total. The administration order was counterbalanced, with half of the participants in each group completing the noun-learning condition on their first session and the verb-learning condition on the second session, while the other half completed the two conditions in reverse order.

2.3.2 Stimuli

All the stimuli were presented using the PsychoPy3 software (Peirce et al., 2019). For each hidden real word, two sentences were presented with an increasing degree of contextual constraint (Mestres-Missé et al., 2010), meaning that the number of acceptable candidates that could replace the new word at the end of the second sentence was lower than in the first sentence. Each sentence was formed by 8 words, with the new word always placed at the end of the sentence. Real noun stimuli and the corresponding sentences were extracted from the materials used in previously published research (Mestres-Missé et al., 2014). The real verbs to be learned were selected from the EsPal database (Duchon, Perea, Sebastián-Gallés, Martí, & Carreiras, 2013) and matched with the previously selected real nouns for word length, word frequency per million, imageability and age of acquisition. Two sentences were built for each verb following the criteria established for the noun's sentences (8-word sentence length and the new word placed at the end). A pilot study with 75 volunteers (age range 19 – 71) was completed prior to this research to ensure at least 80% of correct meaning discovery for the verb duplets, thus matching the statistics for the noun's sentences. All the real words used in this study are listed in the Supplementary Material 1, while the mean values for the psycholinguistic properties of the real words used in each session, as well as the comparison between sessions, can be found in Supplementary Material 2.

A new word (i.e., pseudoword) was created and assigned to every real word to be learned, for a total of 48 new words. An additional set of 48 new words was created to be used as foils in the *Recognition* test (24 foils in each session). All new words respected Spanish phonotactics and were created using the multilingual pseudoword generator Wuggy (Keuleers & Brysbaert, 2010). Pseudoword characteristics, namely length, consonant-vowel structure, neighbourhood count, and mean token frequency were extracted using Clearpond (Marian, Bartolotti, Chabal, & Shook, 2012) and matched between sessions.

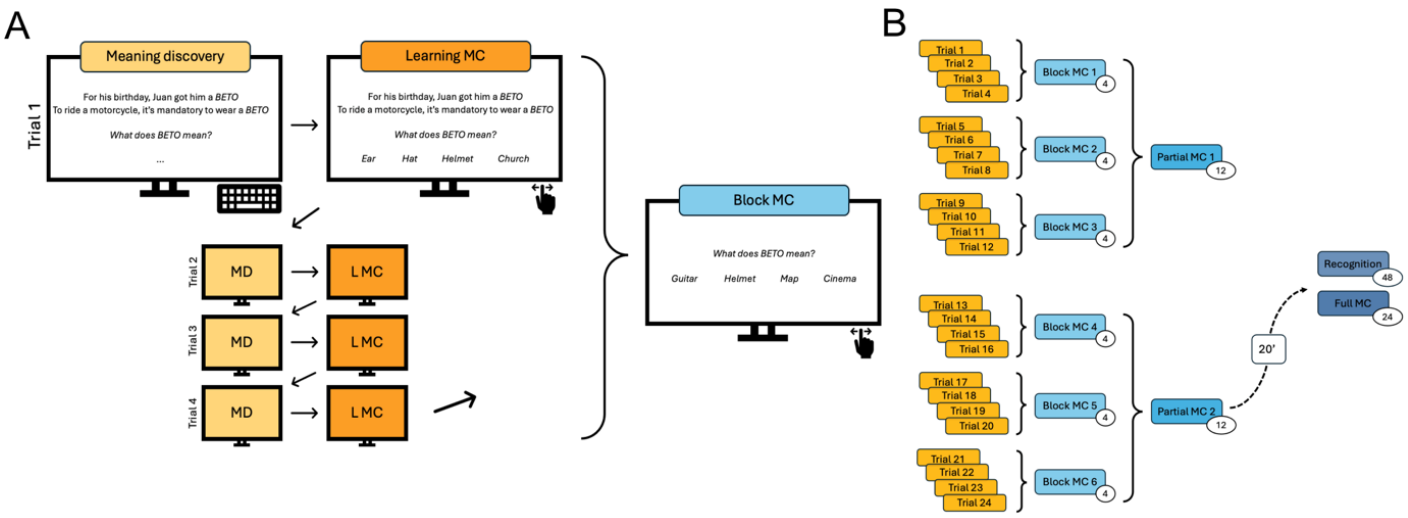

Figure 1 – Design of the Contextual Learning task. Schematic overview of the contextual learning task administered in the study. Warm colors indicate learning tests while cold colors show memory tests. **A.** Example of a learning block. The arrows show the order in which participants are submitted to each test. **B.** Schematic of the entire task. In the memory tests, the number inside the circles indicates the number of words assessed in that test. Abbreviations: MD = Meaning Discovery; L MC = Learning Multiple Choice.

2.3.3 Session procedure

A schematic depiction of the task procedure completed in a learning session and tests can be seen in Figure 1. The procedure was the same on the second session while only changing the condition (nouns or verbs). Importantly, participants provided all responses orally and the experimenter typed them down on the computer to minimize the difficulty of operating the computer keyboard for participants who were unfamiliar with computer use. No time limitations were imposed to the participants in any of the experimental phases nor tests. In each trial, two sentences were presented simultaneously on the computer screen, both ending in the same new word that had to be learned. To reduce working memory load and better adapt the task to our participants, full sentences were presented on the screen instead of the word-by-word sequential presentation applied in previous studies with neurotypical adults (Mestres-Missé et al., 2010). After the presentation of the sentence duplet and with the sentences still on the screen, a message prompted participants to provide the meaning of the new word –hereafter referred to as *Meaning Discovery* test. Immediately after providing a response and with the duplet still shown on screen, participants were asked again for the word meaning while being shown four alternatives: a word conveying the target meaning, a semantically related distractor and two unrelated distractors. This second

test was labeled as *Learning Multiple Choice* (MC) test. The relatedness of semantically close distractors was determined via a questionnaire completed by 35 healthy adults and matched between sessions. During both *Meaning Discovery* and *Learning MC* tests, participants were cued by the experimenter to remember the association between the new word and the learned meaning, but they were not provided with performance feedback. After completing both the *Meaning Discovery* and *Learning MC* tests corresponding to a specific duplet, participants were presented with a new duplet on a new trial.

The 24 trials per session were grouped in blocks of four, with a total of 6 blocks. After the completion of each block and their corresponding learning tests, a memory test for the learned new words was implemented (*Block MC* test). In this test, the sentences were no longer presented on the screen. Instead, memory for the new words learned during that block were tested sequentially by presenting on the screen the prompt-text "what does 'new word' mean?", where 'new word' was substituted by one of the four learned words. Alongside this text, four options were presented including the four target meanings trained during the block, and participants were to select the correct meaning for each new word. The same procedure was carried out to test for a second new word from the block, and so on. After the completion of the *Block MC*, the learning phase continued with the presentation of the first sentence duplet of the next block.

Similarly, another memory test was performed after 3 blocks (12 words learned), testing the recognition of half of the items trained in each session. This *Partial MC* memory test was performed twice per session, at the middle (testing the knowledge of words trained on the first 3 blocks) and at the end (testing the knowledge of words trained in the last 3 blocks).

Immediately after the completion of the entire session, participants performed an unrelated verbal task, used as a distractor, that lasted around 20 minutes. Then, they performed a delayed memory task for learned items which consisted of two parts. First, a *Recognition* test in which 48 single words were presented (24 trained and 24 untrained) and participants were required to judge whether each new word had appeared previously in the learning phase. Finally, they were presented with a *Full MC* memory test, that worked in the same way as the *Block* and *Partial MC*

memory tests, only in this case all 24 learnt items from the session were tested. No feedback was provided to participants in any of the tests.

Importantly, participants were trained before the starting of the real task to ensure that they fully understood the task. Participants were presented with two test trials and performed the Meaning Discovery test and the Learning MC test for each trial. If the response was not correct on both Learning MC tests, participants were explained again the task and presented with two additional test trials. If the response was incorrect again on any of the two Learning MC tests, the administration of the task was stopped, and that participant was not included in the study.

2.3.4 Outcome measures

The outcome measures of the CTXL task were divided into two categories: either learning or memory measures. *Meaning Discovery* and *Learning MC* were designed to test word learning, while the *Block* MC, *Partial* MC, *Full* MC and *Recognition* tests assessed memory.

For the *Meaning Discovery* measure, responses were scored manually by the experimenter. Responses were considered correct when they matched the target or if they were a variation of it or a close synonym, as long as it was semantically and grammatically correct when placed in the sentence. For both learning measures (*Meaning Discovery* and *Learning MC*), an accuracy score was obtained by dividing the correct responses by the total of items to be learned (24 items).

The four remaining tests were considered memory tests because the duplet of sentences did not appear on screen again in any of them, and participants were tested on previously acquired knowledge. For the calculation of memory scores on the memory MCs (*block, partial and full MCs*), only the trials for which participants correctly learned the new word meaning were included, similarly to the methodology used in De Diego-Balaguer et al. (submitted). Trials that were correctly responded in the learning MC were considered as reflective of successful learning performance. Therefore, accuracy scores were calculated by dividing the correctly responded number of items in each test by the total of learned trials in the *Learning MC*. Finally, *Recognition* was measured by calculating the d-prime (d′) index, which reflects an individual's ability to

discriminate new words presented in the learning phase from non-presented new words (pseudowords).

2.4 Neuroimaging data

2.4.1 MRI acquisition

Neuroimaging data was available for a subsample of 13 PwPPA (8 nfvPPA, 5 lvPPA) and 19 NOC. Participants were scanned using a Siemens Prisma Fit 3T scanner with the Syngo MR E11 Software and using a 32-channel head coil at Hospital Clínic, Barcelona (Spain). High-resolution T1 images were acquired using a volumetric magnetization prepared rapid gradient echo (MPRAGE) sequence [repetition time (TR) = 2300 ms; echo time (TE) = 2.98 ms; inversion time (TI) = 900 ms; slice thickness = 1.0 mm; acquisition matrix = 256 x 256; voxel size = 1.0 x 1.0 x 1.0 mm]. Diffusion-weighted images (DWI) were also acquired with a spin-echo echo-planar imaging (EPI) sequence [TR = 7700 ms; TE = 89 ms; 60 axial slices, GRAPPA (generalized autocalibrating partially parallel acquisitions) acceleration factor 2; FOV = 25 cm; flip angle = 90, voxel size = 2 mm3] with one non-diffusion (b = 0 s/mm2) and 30 diffusion weighted volumes (b = 1000 s/mm2). Additional inverse DWI images with equal parameters but opposite phase encoding direction (posterior to anterior) were acquired for the posterior preprocessing and correction of the images, as described in the next sections. The time span between the MRI acquisition and the first task session, as well as a comparison between groups, can be found in Table 1.

2.4.2 Cortical thickness estimation

Cortical thickness was estimated using the Computational Anatomy Toolbox (CAT12) (https://neuro-jena.github.io/cat/, version 2550) in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on MATLAB R2023b (The MathWorks, Inc., 2023). Cortical thickness is provided as a clinical background metric to characterize the atrophy sites of the PwPPA conforming each group. Preprocessing of the T1

images included brain segmentation into grey matter, white matter, and cerebrospinal fluid. Cortical thickness estimation of the right and left hemispheres was based on the projection-based thickness (PBT) method (Dahnke, Yotter, & Gaser, 2013). This involved topology correction, spherical mapping, and spherical registration. Images were visually inspected to ensure data quality and smoothed using a Gaussian kernel of 12mm FWHM (full-width-half-maximum). Subsequently, two-sample *t*-tests were performed between the NOC and PwPPA groups. Reduced cortical thickness was found for both PPA groups compared to NOC (see Figure 2). Cortical thinning for the nfvPPA group was especially widespread in, but not limited to, the left hemisphere. Significant regions included the left opercular IFG, left middle frontal gyrus, bilateral supplementary motor cortices, bilateral precentral gyrus, left IPL, bilateral superior parietal lobule and right temporal pole. Regarding the lvPPA group, decreased thickness was again observed predominantly in the left hemisphere and included the left STG, bilateral MTG, left inferior temporal gyrus, bilateral IPL, bilateral supplementary motor cortices, bilateral precentral gyri and left postcentral gyrus. All reported results were significant at $p < .001$ and thresholded at $k > 50$.

2.4.3 DTI preprocessing

Before preprocessing, all diffusion images were visually inspected by GO using the MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron) to establish the absence of any major defect in the images that could not be addressed in posterior preprocessing steps. All images were pre-processed using the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl/fdt) and the Diffusion Toolkit software (DTK) (Wang et al., 2015). DWI data were processed following these steps: (i) estimation and correction of distortions created by field inhomogeneities by using the topup and applytopup functions from FSL; (ii) eddy current correction using the eddy function from FSL; (iii) brain extraction using FSL Brain Extractor Tool (Smith, 2002; Smith et al., 2004; Woolrich et al., 2009) with 0.2 as threshold value; (iv) reconstruction of the diffusion tensors using DTK (Wang et al., 2015); and (v) whole-brain deterministic tractography using DTK with 35 degrees as maximum curvature and a minimum FA threshold of 0.2.

2.4.4 Tract dissection

Manual deterministic tractography was performed on preprocessed DWI images in native space by using the Trackvis software (v.0.6.0.1, http://trackvis.org/). The white matter tracts dissected were the three segments of the arcuate (AF), namely the direct, anterior and posterior segments; as well as the inferior fronto-occipital (IFOF); the inferior longitudinal (ILF); and the uncinate (UF) fasciculi. Dissections of these tracts were performed by the experimenter bilaterally in every subject by manually delineating Regions of Interest (ROI) as described in previous research (Catani & Thiebaut de Schotten, 2008; Olivé et al., 2023, 2022). After tract dissection, the output measure extracted from every tract and hemisphere was radial diffusivity (RD). A depiction of an example of dissection for an individual is provided in Figure 2.

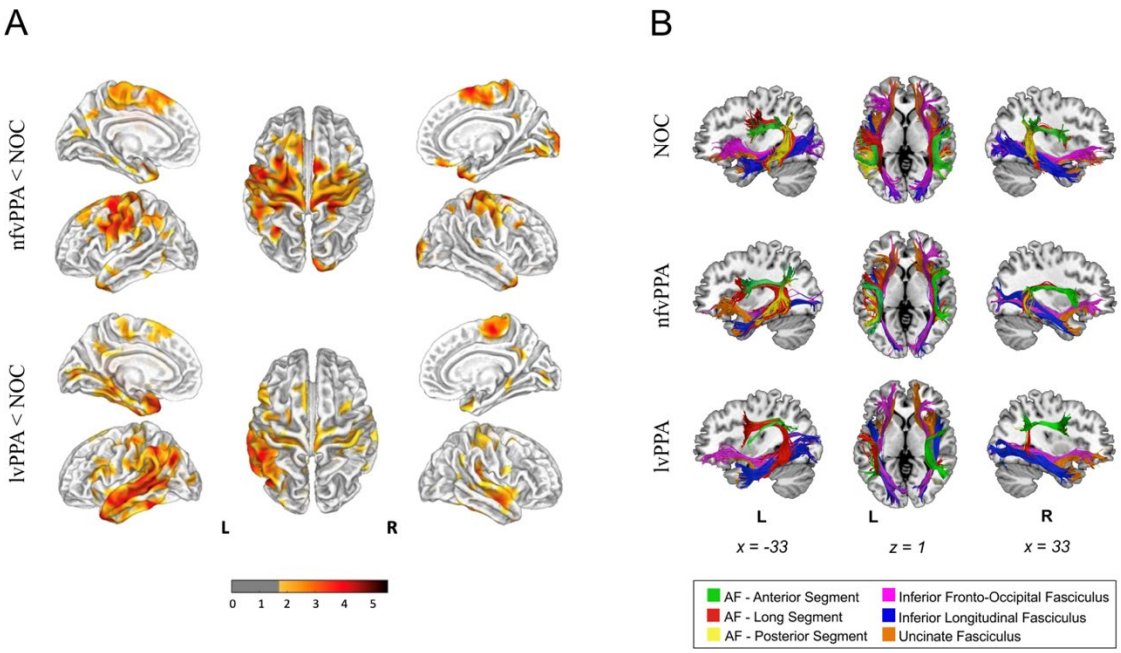

Figure 2 – Neuroimaging results. **A.** Voxel Based Morphometry results showing regions with significant decreases in cortical thickness for the nfvPPA (top row) and lvPPA (bottom row) groups compared with the NOC group. Results have been thresholded at k=50 vertices and $p < 0.05$ (uncorrected for multiple comparisons). The inferior color bar represents the obtained t-scores. **B.** Examples of manual deterministic tractography reconstructions for one participant from each group. Tracts reconstructed were the three segments of the arcuate fasciculus (AF), Inferior Fronto–Occipital Fasciculus, Inferior Longitudinal Fasciculus and Uncinate Fasciculus. Abbreviations: NOC = Neurotypical Older Controls; nfvPPA = Non-fluent variant of Primary Progressive Aphasia; lvPPA = logopenic variant of Primary Progressive Aphasia; L = left; R = Right; AF = Arcuate Fasciculus. Montreal Neurological Institute space coordinates of the structural template slices are specified at the bottom of the image.

2.5 Statistical analysis

2.5.1 Behavioral data

All statistical analyses for the behavioural data were performed using R (R Core Team, version 4.1.0). Models were fitted using the *lme4* package (Bates, Mächler, Bolker, & Walker, 2015) and the results obtained were represented using the *raincloudplots* package. All trials were entered into generalized linear mixed models (GLMMs) to evaluate the likelihood of a correct response (at a single trial level) given the group (independent factor of interest with three levels: NOC, nfvPPA, and lvPPA) in both measures of learning (i.e., *Meaning Discovery* and *Learning MC*). The factor condition (word class: noun vs. verb) was not considered in these initial models. In both learning measures, the dependent variable (i.e., whether the participant had discovered the meaning or not, and whether they had selected the correct meaning out of the four options or not, respectively) was assumed to have a binomial distribution (i.e., correct or incorrect), and therefore, a logit link function was applied. Random intercepts for participant and item were included in all GLMMs to account for differences driven by individual participant and item characteristics. Thus, the structure of these models was: response (correct/incorrect) ~ group + (1|participant) + (1|item). When needed, post-hoc analyses were conducted via t-test comparisons to identify the groups that showed significant differences, using the False Discovery Rate (FDR) to correct p-values (*emmeans* package; Lenth, Singmann, Love, Buerkner, & Herve, 2018).

Similarly, GLMMs were used to assess whether the three groups (NOC, nfvPPA, and lvPPA) showed differences in their performance on the multiple-choice memory tasks (i.e., *Block, Partial* and *Full MC* tests). GLMMs followed the same structure as for the learning tasks [i.e., response (correct/incorrect) ~ group + (1|participant) + (1|item)]. Importantly, only learned trials (as trials that were correctly inferred in the *Learning MC* test) were included in these memory analyses. For the *Recognition* task, d-prime scores were computed. Then, a one-way ANOVA with group as between subject factor (three levels: NOC / nfvPPA / lvPPA) was performed to test differences in d-prime scores between groups.

Additionally, the effect of condition (word class: noun vs. verb) of the hidden meanings on the likelihood of correct responses was assessed. To this end, all models were rebuilt including the interaction between word class and group [i.e., response (correct/incorrect) ~ group * word class + (1|participant) + (1|item)]. Moreover, for models in which the word class by group interaction revealed no significant effects, the main fixed effect of word class was further checked by a simplified model [i.e., response (correct/incorrect) ~ group + word class + (1|participant) + (1|item)]. For the *Recognition* task, a repeated measures ANOVA was performed with condition as the within-subject factor (two levels: d'-nouns/d'-verbs) and group as the between-subject factor (three levels: NOC/nfvPPA /lvPPA). The same statistical models were built to compare the performance between the NOC and NYC groups in order to assess the validity of the task.

2.5.2 Neuroimaging and behavioral data analysis

An exploratory analysis was performed to uncover the association between CTXL performance in PPA and language-related white matter tract integrity. To this end, Spearman correlations were performed between the *Meaning Discovery* measure and RD values extracted from the different white matter tracts dissected. Given the limited sample size and the exploratory nature of the analysis, we included all participants in the correlations (NOC and individuals with PPA regardless of their PPA diagnostic group classification). A False Discovery Rate (FDR) correction was used to adjust for multiple comparisons and all reported *p*-values are corrected.

3. Results

3.1 Learning Measures

First, when predicting the likelihood of correctly inferring the meaning of the pseudowords, the GLMM [response ~ group + (1|participant) + (1|item), $\chi^2(1) = 7.38$, p = .007, AIC = 1724, LL = -858] revealed a better performance by NYC than NOC group (z-ratio = 2.87, p = .004). However, when comparing the performance for the *Learning MC* test, the GLMM [response ~ group +

(1|participant) + (1|item), $\chi^2(1) = .5896$, p = .4426, AIC = 255, LL = -123] showed no significant differences between the two groups, which could be due to a ceiling effect in both groups (mean group accuracy: NOC = 0.99 ± 0.016; NYC = 0.99 ± 0.020).

Contrast	Estimate	SE	Z-ratio	p value
Meaning Discovery test				
NYC – NOC	0.56	0.20	2.87	**0.004**
NOC – nfvPPA	1.30	0.35	3.77	**0.0002**
NOC – lvPPA	3.20	0.37	8.58	**< 0.0001**
nfvPPA – lvPPA	1.89	0.41	4.58	**< 0.0001**
Learning MC test				
NYC – NOC	-0.55	0.72	-0.76	0.448
NOC – nfvPPA	2.56	0.74	3.47	**0.0008**
NOC – lvPPA	3.93	0.74	5.33	**< 0.0001**
nfvPPA – lvPPA	1.37	0.67	2.05	**0.0404**
Block MC test				
NYC – NOC	0.94	0.257	3.64	**0.0003**
NOC – nfvPPA	0.51	0.175	2.96	**0.0046**
NOC – lvPPA	0.75	0.192	3.92	**0.0003**
nfvPPA – lvPPA	0.23	0.218	1.08	0.2825
Partial MC test				
NYC – NOC	1.06	0.24	4.45	**< 0.0001**
NOC – nfvPPA	0.43	0.20	2.15	**0.0470**
NOC – lvPPA	0.52	0.22	2.40	**0.0470**
nfvPPA – lvPPA	0.09	0.25	0.36	0.7179
Full MC test				
NYC – NOC	0.84	0.28	3.06	**0.0022**
NOC – nfvPPA	0.30	0.20	1.47	0.2138
NOC – lvPPA	0.40	0.22	1.79	0.2138
nfvPPA – lvPPA	0.10	0.25	0.38	0.7055

Table 2 -Contextual learning task results. Results from the different subtest of the the CTXL task. Statistically significant group differences are marked in bold. Abbreviations: MC = Multiple choice; SE = Standard error; NYC = Neurotypical Younger Controls; NOC = Neurotypical Older Controls; nfvPPA = Non-fluent variant of Primary Progressive Aphasia; lvPPA = logopenic variant of Primary Progressive Aphasia.

When comparing PPA with NOC groups, the first analysis also focused on group differences in the *Meaning Discovery* accuracy. The model [response ~ group + (1|participant) + (1|item), $\chi^2(2) = 45.9$, $p = 1.1x10^{-10}$, AIC = 1823, LL = -907] revealed significant differences between the three groups: both nfvPPA and lvPPA performed worse than NOC (z-ratio = -3.77, p = .0002, and z-ratio = -8.58, p < .0001, respectively) while lvPPA performed worse that nfvPPA (z-ratio = -4.58, p < .0001). Then, group differences in the *Learning MC* test were analyzed. The GLMM [response ~ group + (1|participant) + (1|item), $\chi^2(2) = 29.2$, $p = 4.7x10^{-7}$, AIC = 632, LL = -311] showed

significant differences between the three groups. Similar to our findings for the *Meaning Discovery* test, accuracy in the *Learning MC* for both nfvPPA and lvPPA was worse compared to that of the NOC (z-ratio = -3.47, p = .0008, and z-ratio = -5.33, p < .0001, respectively), and lvPPA performed worse than nfvPPA (z-ratio = -2.05, p = .04). See Figure 3 for a comparison of learning measures between groups and Table 2 for a summary of the results from the group comparisons.

Figure 3 – Learning results from the contextual learning task. Accuracy scores from the learning measures of the contextual learning task depicted for each group (yellow diamonds represent NYC, green circles are the NOC, orange squares correspond to nfvPPA and purple triangles show lvPPA participants). Each measure is represented in three different manners from left to right: individual participant's scores, group values in a boxplot and group distribution. The asterisk symbol (*) indicates statistical difference between compared groups with P value lower than 0.05. The left part shows the accuracy scores from the meaning discovery test, the right side shows the accuracy scores from the learning multiple choice test. Abbreviations: NYC = Neurotypical Younger Controls; NOC = Neurotypical Older Controls; nfvPPA = Non-fluent variant of Primary Progressive Aphasia; lvPPA = logopenic variant of Primary Progressive Aphasia.

On the other hand, the models did not reveal any significant effect for word class when comparing NYC and NOC, either when assessing the interaction with group (*Meaning Discovery*: χ^2 (2) = .62, p = .43; *Learning MC*: χ^2 (2) = .78, p = .38) or the main effect (*Meaning Discovery*: χ^2 (2) = .019, p = .89; *Learning MC*: χ^2 (2) = 2.44, p = .12) for any of the measures.

However, when comparing NOC and PPA groups, the models assessing the interaction between group and word class showed a significant interaction effect for the *Meaning Discovery* test (χ^2 (2) = 12.21, p = .0022), suggesting a difference in learning nouns or verbs across groups.

Subsequently, post-hoc analyses revealed significant differences only in the lvPPA group, in which nouns were worse learnt than verbs (z-ratio = -2.45, p = .014). In contrast, no significant interaction nor main effect for word class was found in the *Learning MC* test (χ^2 (2) = .0827, p = .96 and χ^2 (2) = .72, p = .40, respectively), indicating no significant differences in learning nouns versus verbs in general or within groups.

3.2 Memory Measures

As for the memory measures, GLMMs comparing older and younger NC revealed the same direction of results for all memory tests, meaning NOC performed significantly worse than NYC in the *Block MC* (χ^2 (1) = 12.1, p = .0005, AIC = 3084, LL = -1538; z-ratio = -3.64, p = .0003), *Partial MC* (χ^2 (1) = 17.16, p = 3.44 x10^{-5}, AIC = 3197, LL = -1595; z-ratio = -4.45, p < .0001), and *Full MC* (χ^2 (1) = 8.73, p = .0031, AIC = 3142, LL = -1567; z-ratio = -3.06, p = .0022). Likewise, *Recognition* was worse in older than younger NC (t(50) = 2.23, p = .03).

On the other side, the GLMM comparing NOC and PPA groups for the *Block MC* test [response ~ group + (1|participant) + (1|item), χ^2 (2) = 16.5, p = .0003, AIC = 2561, LL = -1275] revealed worse performance of both PPA groups (nfvPPA and lvPPA) compared to NOC (z-ratio = -2.96, p = .005, and z-ratio = -3.92, p = .0003, respectively), although no significant differences were found between nfvPPA and lvPPA in this case (z-ratio = -1.08, p = .283, see Figure 4). The same pattern was observed for the *Partial MC*, where the GLMM [response ~ group + (1|participant) + (1|item), χ^2 (2) = 7.56, p = .0228, AIC = 2484, LL = -1237] showed that both nfvPPA and lvPPA groups performed worse than NOC (z-ratio = -2.15, p = .047, and z-ratio = -2.40, p = .047, respectively) but no significant differences were found between them (z-ratio = .361, p = .718, see Figure 4). Contrastingly, the results for the *Full MC* [response ~ group + (1|participant) + (1|item), χ^2 (2) = 3.98, p = .136, AIC = 2424, LL = -1207] did not reveal any significant differences between any of the three groups (see Table 2 for detailed statistical measures). Finally, the pattern of results was slightly different for the *Recognition* tests, showing a statistically significant effect

of group (F(2,39) = 10.96, p < .001). Post-hoc analyses revealed significantly worse performance of the lvPPA group compared to NOC (t(27) = 1.05, p < .001) and nfvPPA (t(17) = 2.84, p = .011) for discriminating old from new pseudowords, while no differences were found between NOC and nfvPPA (t(30) = 1.33, p = 194).

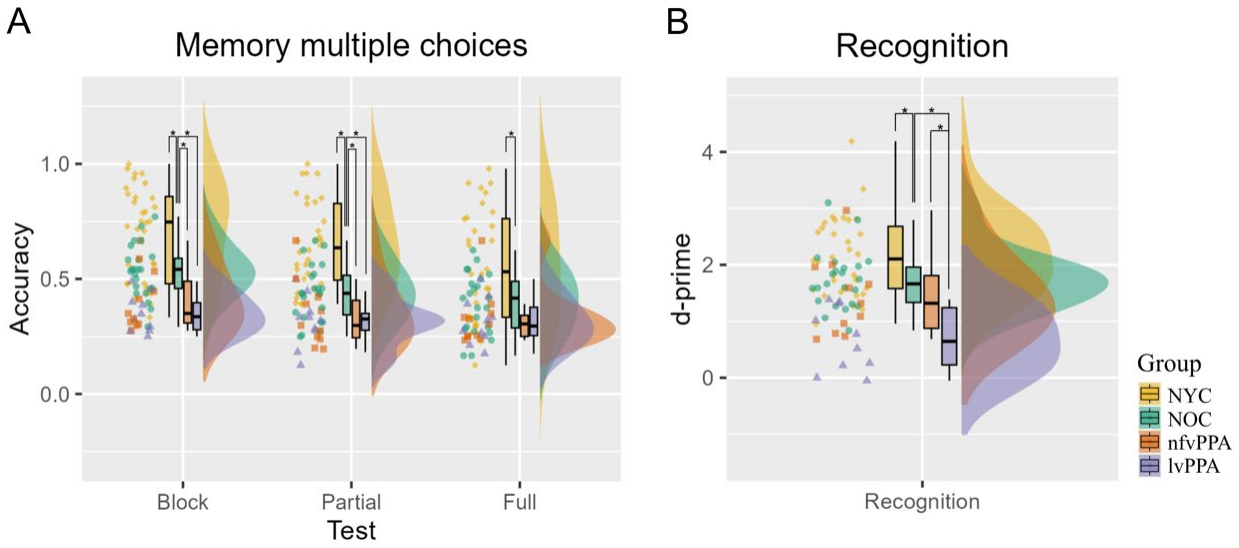

Figure 4 – Memory results from the contextual learning task. Accuracy scores from the memory measures of the contextual learning task depicted for each group (yellow diamonds represent NYC, green circles are the NOC, orange squares correspond to nfvPPA and purple triangles show lvPPA participants). Each measure is represented in three different manners from left to right: individual participant's scores, group values in a boxplot and group distribution. The asterisk symbol (*) indicates statistical difference between compared groups with P value lower than 0.05. **A.** Accuracy scores from the memory multiple choice tests. All trials from each subject are represented together, without discriminating by word class. Tests represented are, from left to right: block multiple choice, partial multiple choice, and full multiple choice **B.** D-prime scores from the recognition tests. Again, all trials from each subject are represented together, without separating them by word class. Abbreviations: NYC = Neurotypical Younger Controls; NOC = Neurotypical Older Controls; nfvPPA = Non-fluent variant of Primary Progressive Aphasia; lvPPA = logopenic variant of Primary Progressive Aphasia.

The word class effect was then explored in memory measures. When comparing NYC and NOC, only the *Partial MC* showed a significant interaction between group and word class (χ^2 (2) = 5.299, p = .021) although post-hoc analysis did not reveal differences within any group in recalling nouns or verbs (NYC: z-ratio = -0.75, p = .46; NOC: z-ratio = 1.47, p = .14). Neither the *Block MC* nor the *Full MC* revealed any significant interaction effect (*Block MC*: χ^2 (2) = 3.56, p = .059; *Full MC*: χ^2 (2) = .14, p = .70). When comparing NOC and PwPPA, the interaction between group and word class was not significant for any of the memory multiple choice tests (*Block MC*: χ^2 (2) = .52, p = .77; *Partial MC*: χ^2 (2) = 2.12, p = 0.35; *Full MC*: χ^2 (2) = .52, p = .77). Similarly, the main effect of word class was not significant in any of the multiple choice

tests either when comparing NYC and NOC (*Block MC*: χ^2 (2) = .23, p = .64; *Partial MC*: χ^2 (2) = .083, p = .77; *Full MC*: χ^2 (2) = 2.39, p = .12) nor when comparing NOC and PPA groups (*Block MC*: χ^2 (2) = 1.41, p = .23; *Partial MC*: χ^2 (2) = 1.90, p = .17; *Full MC*: χ^2 (2) = 2.53, p = .11).

Finally, the word class effect was evaluated for *Recognition* by a repeated measures ANOVA. No significant interaction effect for word class was found when comparing NYC and NOC (F(1,50) = 1.78, p = .188). The main effect of word class, however, was statistically significant (F(1,50) = 20.11, p < .001). Post-hoc analyses revealed that the *Recognition* of nouns was better than the *Recognition* of verbs in both groups (NYC: t(30) = 2.41, p = .022; NOC: t(20) = 3.94, p = .001). Similarly, the interaction between group and word class was not significant when comparing NOC and PwPPA (F(2,37) = .35, p = .707) whereas the main effect of word class was again statistically significant (F(1,37) = 15.74, p < .001). The pattern of results might reflect a general better *Recognition* of nouns versus verbs in all groups. This effect was confirmed by post-hoc analyses, which revealed a better *Recognition* of nouns compared to verbs in NOC (t(20) = 3.94, p = .001) and nfvPPA (t(11) = 2.44, p = .035), whereas no significant differences were found in lvPPA (t(8) = 1.23, p = .26).

3.4 Meaning discovery and white-matter integrity (radial diffusivity)

The correlational analysis uncovered several statistically significant FDR-corrected results. Specifically, participants' *Meaning Discovery* accuracy values correlated with RD values from two dorsal language tracts: the long segment (r_s = -.485, p = .02) and the anterior segment of the left arcuate fasciculus or AF (r_s = -.485, p = .027). With respect to the RD values from the ventral language tracts, the significant associations that emerged with *Meaning Discovery* accuracy were those in the left IFOF (r_s = -.414, p = .043), as well as both the left UF (r_s = -.516, p = .012) and right UF (r_s = -.545, p = .012). See Figure 5 for a depiction of the significant correlations obtained.

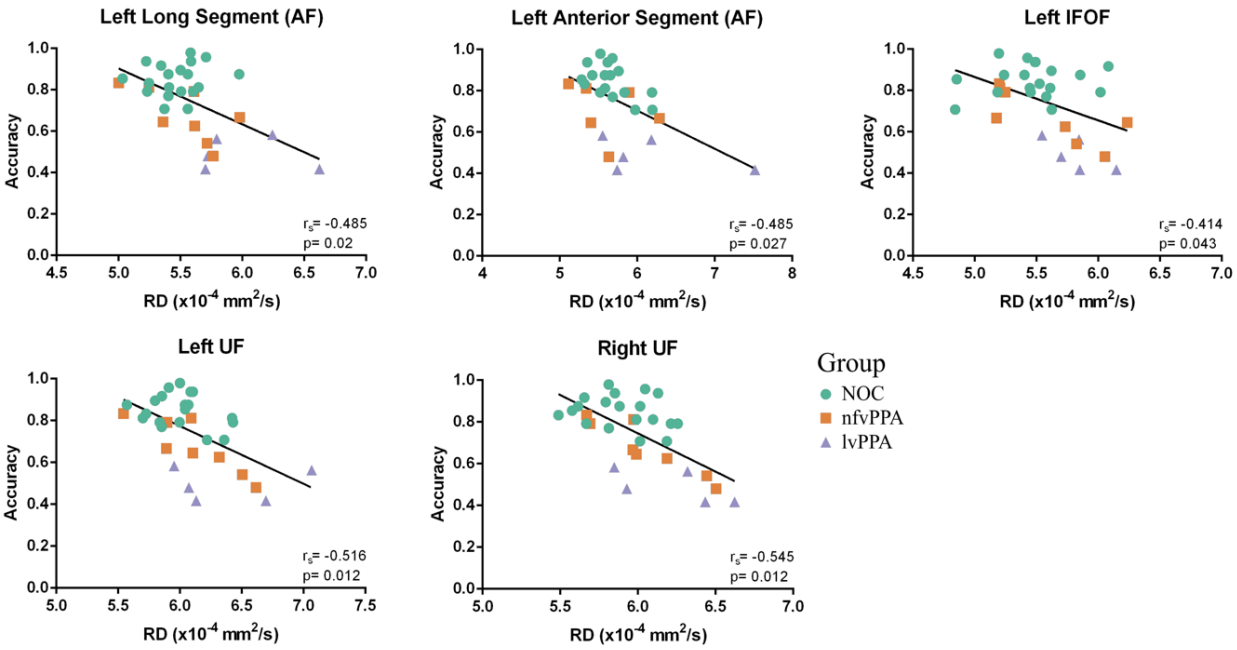

Figure 5 – Significant correlations between meaning discovery and white matter tracts' microstructure. Significant spearman correlations between meaning discovery accuracy scores and radial diffusivity from white matter tracts. Lower RD values are generally associated with better white-matter microstructure. All results shown are FDR-corrected. Abbreviations: AF = Arcuate Fasciculus; IFOF = Inferior Frontal Occipital Fasciculus; UF = Uncinate Fasciculus; RD = Radial Diffusivity. Abbreviations: NOC = Neurotypical Older Controls; nfvPPA = Non-fluent variant of Primary Progressive Aphasia; lvPPA = logopenic variant of Primary Progressive Aphasia.

4. Discussion

The main aim of this study was to investigate the integrity of WL ability in PPA. To this end, we adapted a CTXL task previously used with neurotypical individuals (De Diego-Balaguer et al., submitted; Mestres-Missé et al., 2014; Ripollés et al., 2014). The task required participants to infer the meaning of a new word from the context provided in each duplet of sentences and map the extracted concept into each new word form. We then assessed CTXL ability and subsequent memory performance for trained items in two variants of PPA – nfvPPA and lvPPA– which we compared to a group of NOC.

Our findings revealed that the novel word learning ability of PwPPA was below that of NOC in both learning measures, namely the *Meaning Discovery* and *Learning MC* tests. The difficulties observed in PwPPA in the CTXL task might be explained by the cognitive requirements that

novel word learning places on learners as it relies on several abilities including language processing and memory, among others (Peñaloza et al., 2022). According to neuroanatomical models of word learning (Rodriguez-Fornells et al., 2009), a successful CTXL process mainly requires the recruitment of two interfaces in a coordinated manner: (i) the dorsal auditory-motor interface, related to the encoding of a new word form, and (ii) the ventral meaning-integration interface, required to infer the meaning of a word from context and attaching this concept to the new word. Thus, CTXL relies on a wide cerebral word-learning network comprising prefrontal, middle temporal, and inferior parietal regions, as well as the anterior cingulate cortex, basal ganglia, and the medial temporal lobe (Mestres-Missé et al., 2010). Some of these important regions for CTXL typically undergo degeneration in PwPPA especially the STG, MTG and IPL in lvPPA, and the IFG in nfvPPA. Therefore, the atrophy patterns of both PPA subtypes might put the crucial interfaces for word learning at risk, such that an impairment in CTXL was to be expected, in contrast to the expected successful learning performance of NOC. Moreover, these results resemble those observed in some PSA patients, in whom significant impairments compared to NOC have been reported in various WL tasks (Peñaloza et al., 2015, 2017), as well as the impaired grammar learning reported for nfvPPA (Cope et al., 2017).

However, even more interesting is the remarkable difference found here between PPA groups in the learning tests, namely the *Meaning Discovery* and *Learning MC* tests. Specifically, nfvPPA showed higher accuracy in both tests compared to lvPPA participants. Even if previous studies have reported specific deficits in lvPPA compared to other PPA subtypes on various aspects such as naming, repetition, or memory (Butts et al., 2015; Eikelboom et al., 2018; Gorno-Tempini et al., 2008), WL ability had not been previously assessed nor compared between these two PPA variants. The interpretation of this novel result asks for a review of the affected regions in each PPA subtype and their presumed role in the task. As discussed above, neurodegeneration in lvPPA typically affects left temporoparietal regions, mainly the STG, MTG, and IPL (Jonathan D. Rohrer et al., 2013). The MTG, proposed as a key site for semantic processing (Turken & Dronkers, 2011), has also been proposed as an essential region for the mapping between semantic features and phonetic units (Gow, 2012; Hickok & Poeppel, 2007; Rodriguez-Fornells et al.,

2009), which probably explains why this region has been linked repeatedly with the CTXL task (Mestres-Missé et al., 2010; Ripollés et al., 2017, 2014). Likewise, the STG has been linked with phonological processing of word representations (Hickok & Poeppel, 2007; Rodriguez-Fornells et al., 2009), and a more recent investigation identified the left STG, jointly with the angular gyrus, as crucial sites for the early stages of verbal learning (Afthinos et al., 2022). Finally, the IPL has been related to word-form processing, and its stimulation with high-definition transcranial direct current stimulation seems to improve novel word learning in healthy participants (Perceval, Martin, Copland, Laine, & Meinzer, 2017). Similarly, grey matter density in the IPL has been observed to be higher in bilinguals compared to monolinguals, and to be positively correlated with second-language proficiency (Abutalebi, Canini, Della Rosa, Green, & Weekes, 2015; Mechelli et al., 2004). Overall, the commonly affected cortical sites in lvPPA are crucial regions involved in WL. Therefore, it is expected that the degeneration of this cortical network would largely disrupt the complex WL machinery and would explain the substantial decrease in learning accuracy scores observed in this group.

On the other hand, previous studies have reported structural and functional abnormalities in nfvPPA in different brain regions, including the frontal gyri, precentral gyrus, supplementary motor area and the anterior insula (Gorno-Tempini et al., 2011; Mandelli et al., 2018; Tu et al., 2015). From these, the IFG is of special interest for the current study, due to its association to semantic processing, and the top-down selection of the best-fitting lexical candidate in case of competing alternatives, specifically (Hoffman, Jefferies, Ehsan, Hopper, & Ralph, 2009; Navarrete-Orejudo et al., 2023; Ripollés et al., 2017; Thompson-Schill & Botvinick, 2006). Considering the putative functions of the IFG, it is reasonable to assume that its alteration impacts CTXL performance. Our discovery of decreased accuracy in learning scores in nfvPPA seem to support this notion, even though its impact in CTXL should be lower compared to that of lvPPA. NfvPPA individuals might produce some errors, potentially due to an incorrect selection of an unrelated word or a lack of inhibition of lexical competitors. However, this should not affect their ability to activate relevant semantic features or to infer the meaning of the new word, so in many cases they might still be able to produce a correct response.

The IPL and the IFG are regions affected in lvPPA and nfvPPA, respectively, and are both associated with verbal Short-Term Memory (vSTM) (Martin et al., 2021; Olivé et al., 2023; Perceval et al., 2017), a crucial cognitive ability involved in WL (Rodriguez-Fornells et al., 2009) which also predicts word learning ability in PSA (Navarrete-Orejudo et al., 2023; Peñaloza et al., 2015, 2016). Previous studies have reported lower performance from lvPPA compared to nfvPPA in this domain (Gorno-Tempini et al., 2011; Rohrer et al., 2010). Thus, variations in vSTM ability could explain the differences on CTXL between variants. However, one of the adaptations made to the current task compared to previous studies (Mestres-Missé et al., 2014; Ripollés et al., 2017) was the presentation of whole-sentence duplets on-screen for the entire duration of the learning trials. The aim of this modification was to minimize the vSTM load of the task and therefore its effects on performance should be minimal and might not be sufficient to explain the differences found between the groups.

Another important modification we made to the current task was the inclusion of various memory measures that would allow us to track the strength of the new memory traces formed for the learned items over time. Noticeably, there were no differences between PwPPA in these memory tasks. This dissociation between learning ability and the capacity to encode and consolidate new information in PPA patients speaks in favor of the importance of measuring both aspects in this clinical population: the acquisition of new information versus the strength of new memories formed. In the same vein, further research should explore the integrity of these partially independent neural networks, that contribute to WL and the information transfer to long-term memory, in PwPPA.

Several reasons could account for the similarities we have observed here between PPA groups in the memory tests. The most straightforward one would be that there are indeed no differences between PPA groups in terms of memory for verbal information. However, with the current experimental design, we cannot rule out the possibility that the absence of differences is due to the correction method used. Specifically, only the successfully learnt items (correct responses in the *Learning MC*) have been considered for the *Memory MCs*. Thus, even if the

accuracy is similar for nfvPPA and lvPPA, the absolute number of correct items is higher in the nfvPPA. Nonetheless, this result seems to indicate that between-group differences are mostly concentrated in the initial stages of WL, rather than in the memory process associated with those learnt items.

The *Recognition* test needs to be interpreted independently from the other memory tests because it measures different processes. Specifically, this test measures the memory of trained novel word forms instead of assessing the strength of the association between the learnt new words and their meanings. Here, the results reveal a lower performance in lvPPA participants compared to both nfvPPA and NOC participants. These data align with PSA findings, that identify phonological *Recognition* correlates in the superior temporal and posterior parietal regions (Alyahya, Halai, Conroy, & Lambon Ralph, 2018), which greatly overlap with typically damaged cortical sites in lvPPA. Thus, our findings of significant cortical thinning over left STG and bilateral IPL in lvPPA compared to NOC would explain the deficits present in this group for new-word *Recognition*, as well as the comparable performance between the nfvPPA and NOC groups.

It is important to highlight that a significant difference was consistently found across tests between the older and the younger NC groups. NYC performed better in all cases, except in the *Learning MC* test because the performance of both NC groups was practically at ceiling. Such differences were to be expected, given the extensively reported age-related effect in learning and memory (D'Eredita & Hoyer, 1999; Kvavilashvili, Kornbrot, Mash, Cockburn, & Milne, 2009; E. Service & Craik, 1993; Ward, Berry, & Shanks, 2013). Additionally, the excellent accuracy of the NYC In practically all tests ensures the validity and feasibility of the task.

We further examined if the word class from the learnt words (nouns vs verbs) determined its learning success or subsequent memory performance. The results showed no differences in learning or memory test success between nouns and verbs in any of the groups. The only exceptions were (i) significantly greater *Meaning Discovery* of verbs compared to nouns in the *Meaning Discovery* test only in lvPPA, and (ii) statistically significant better *Recognition*

accuracy of nouns relative to verbs for the NCs (both NYC and NOC) and nfvPPA. While the comparison of learning success between word classes was only exploratory, it does represent a relevant element of study. The results provide information on a topic that has generated a growing interest in the literature in recent years, although previous reports have originated conflicting results on the matter. Specifically, some authors have argued that nouns and verbs are processed and learned differently, recruiting distinct brain regions (Lukic et al., 2021; Mestres-Missé et al., 2010; Shapiro et al., 2005), which would account for dissociations frequently observed in aphasic patients (Crepaldi et al., 2006; Hillis & Caramazza, 1995). On the contrary, others claim that these grammatical categories are processed similarly and that the previously reported differences may be associated with multiple methodological factors such as insufficient matching of linguistic variables or diversity in the linguistic processes evaluated (Alyahya et al., 2018; Vigliocco et al., 2011). The stimuli in our task were carefully matched across conditions accounting for several psycholinguistic variables including word frequency, imageability, age of acquisition and length. We did not find consistent differences according to grammatical class so the results from the present study align with the latter trend. Thus, it seems like nouns and verbs can be learned and remembered similarly by both NOC and PwPPA in these experimental settings, provided that the psycholinguistic variables of the words to be learned are rigorously matched.

In the same vein, verbs have been considered to be harder to process and learn because of their more relational and abstract nature, making these processes more dependent on the integration of the contextual clues for verbs compared to nouns (Mestres-Missé et al., 2010). Nevertheless, the context availability theory states that abstract and concrete words are processed equally well if enough external semantic context is provided (Wattenmaker & Shoben, 1987). Although that theory was originally suggested and tested for the concreteness effect (Schwanenflugel, Harnishfeger, & Stowe, 1988; van Hell & de Groot, 1998), it could also apply for the word class effect examined here. The design of the current task, in which duplets of sentences were provided as context for each new word, ensured that a sufficient supporting framework and semantic priming was provided in all cases to reduce the potential effect of word class.

Finally, we conducted exploratory analyses to examine the structural brain connectivity related to CTXL. White matter tracts are a crucial anatomical element to consider when studying brain networks and can provide valuable information about the nature and progression of different PPA variants (Mahoney et al., 2013) with regards to specific processes such as CTXL. Despite previous suggestions of larger white matter than grey matter alterations in PPA (Agosta et al., 2013; Galantucci et al., 2011), the knowledge about white matter abnormalities in this population is still limited and contrasts with the extensive literature concerning the characterization of grey matter anomalies (Galantucci et al., 2011; Gorno-Tempini et al., 2011; Mahoney et al., 2013; Pereira et al., 2009; Rohrer et al., 2009, 2010, 2013; Tee & Gorno-Tempini, 2019). For this analysis, *Meaning Discovery* was chosen as the variable of interest because it was the purest measure of learning, given that it required a spontaneous response from participants following their first exposure to each duplet of sentences. Also, it was an open question, meaning that the answer given by participants was not influenced by any of the possible options presented in the MC tests, which could help narrow down the meaning inference process. On the other hand, RD is a microstructural measure commonly used in DTI studies (Elmer et al., 2019; Olivé et al., 2022). Increases in RD have been related to several factors such as decline in axon density and myelination (Aung et al., 2013), serving as an indicator of signal-conduction efficiency along the axons of the studied tracts (Fields, 2008; Zatorre et al., 2012). Moreover, RD has been used in studies investigating the structural underpinnings of WL both in healthy (López-Barroso et al., 2013; Ripollés et al., 2017) and clinical populations (Baijot et al., 2022). Critically, the RD of different white matter tracts has also been previously compared between PPA variants (Mahoney et al., 2013), showing an increase of RD in left ventral tracts (UF and ILF) in both nfvPPA and lvPPA groups, as well as an increase in a left dorsal (superior longitudinal fasciculus) and two right ventral tracts (UF and ILF) only in the lvPPA when compared to a NOC group. These results point to a differential pattern of white matter degeneration for each variant, which could impact the ability of PwPPA to perform tasks such as the CTXL.

Our results show a relationship between *Meaning Discovery* accuracy and RD in both ventral (left IFOF and bilateral UF) and dorsal (long and anterior segments of the left arcuate) tracts. First, the

results link learning success to the left IFOF and both left and right Ufs. These two tracts belong to the ventral language stream, which is usually associated with semantic processing (Hickok & Poeppel, 2007). The task presented in this study has a clear semantic component and requires individuals to detect the semantic cues embedded in the sentences and integrate the information to discover the hidden meaning of the new word. Hence, the emergence of ventral tracts in relationship to CTXL is expected. Moreover, it aligns with previous studies that found an association between CTXL performance and the microstructure of ventral tracts: the IFOF, the UF, and the ILF, specifically (Ripollés et al., 2017, 2014). Secondly, our results also show a relationship between *Meaning Discovery* and two segments of the arcuate fasciculus, which belong to the dorsal language stream. The most plausible explanation for this finding is that a successful learning in this task does not only require the extraction of the hidden meaning of the word, but also the association of said meaning with the corresponding new word. This demands the processing and encoding of the new word's form, through articulation mapping and phonological processing, which have generally been associated with dorsal language tracts (Dick et al., 2014; López-Barroso et al., 2013). Consistently, the integrity of portions of this tract has been previously linked to performance in the CTXL (Ripollés et al., 2014), and other WL tasks (López-Barroso et al., 2013; Ripollés et al., 2017). Overall, these findings emphasize the complex nature of WL, in which the recruitment and proper functioning of a large part of the language-processing network is necessary to achieve a satisfactory result. It also indicates that there is a relationship between the integrity of language tracts and performance in this task.

We acknowledge some limitations in the current research, including a limited sample size for PPA groups. However, PPA is a rare disease, which complicated the recruitment of participants meeting the inclusion and exclusion criteria and who were available and willing to undergo multiple sessions to perform our experimental task and additional assessments. On the other hand, the results from the present study raised some questions deserving of follow-up examination. For instance, studying in more depth the results of the secondary objectives (absence of learning differences between nouns and verbs, or the structural neural underpinnings of CTXL) by using

tasks and paradigms specifically designed for these purposes. Furthermore, the cognitive correlates of CTXL could also be explored in PPA to better understand how processes such as semantic processing ability, verbal short-term memory, or attention contributed to the differences found in this task. Although initially we attempted to also include individuals with the semantic variant of PPA in this study, their recruitment for comparable sub-group sample sizes proved rather challenging. Future studies should be inclusive of svPPA participants to assess their CTXL ability, comparing it to that of nfvPPA and lvPPA groups. Given that this WL task addresses semantic learning, it might have clinical value to improve the diagnostic classification of this PPA variant. Moreover, given that damage of the Anterior Temporal Lobe (ATL) is consistently observed in svPPA, assessing this population would provide additional information regarding the role of the ATL in CTXL, as well as the role of linked structures within this network such as the IFG and MTG regions, or the UF and ILF tracts.

Despite these limitations, results from the present work provide relevant and novel information that can help to better understand PPA across different subtypes.

2. Conclusions

Our results revealed that contextual word learning is possible yet impaired in individuals with PPA compared to neurotypical controls. Moreover, differences emerged between PPA groups, with nfvPPA showing higher learning accuracy than lvPPA. The present study constitutes the first attempt to characterize the integrity of contextual word learning ability in PPA, and thus its results are of great relevance for the characterization of cognitive abilities in individuals with this condition.

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7. Supplementary material

Supplementary material 1 – List of words used in the experiment along with their English translation.

Nouns:
Calendario (calendar); Mapa (map); Espejo (mirror); Casco (helmet); Cocina (kitchen); Aeropuerto (airport); Hotel (hotel); Cuadro (painting); Guitarra (guitar); Barco (boat); Fuego (fire); Cine (cinema); Trozo (slice); Norma (rule); Pecado (sin); Ganas (desire); Eco (echo); Cuidado (attention); Culpa (guilt); Error (error); Curso (course); Inteligencia (intelligence); Motivo (motive); Prueba (test).

Verbs:
Florecer (to bloom); Descansar (to rest); Cerrar (to close); Cortar (to cut); Comprar (to buy); Votar (to vote); Matar (to kill); Estudiar (to study); Salvar (to save); Ganar (to win); Entrar (to enter); Trabajar (to work); Aguantar (to hold); Aclarar (to clarify); Apuntar (to aim); Olvidar (to forget); Dedicar (to dedicate); Quedar (to meet); Actuar (to act); Aumentar (to increase); Permitir (to allow); Proteger (to protect); Mejorar (to improve); Conocer (to know).

Psycholinguistic variable	Nouns	Verbs	T test	p value
Frequency per million	53.07 + 33.75	44.47 + 31.31	0.915	0.365
Familiarity	5995.63 + 544.17	5991.63 + 479.98	0.027	0.979
Imageability	4858.48 + 1494.50	4393.25 + 1052.51	1.229	0.226
Age of Acquisition	5.38 + 1.21	5.65 + 1.19	0.771	0.446
Word length (number of letters)	6.00 + 2.10	6.88 + 1.12	1.813	0.076

Supplementary material 2 – Comparison of psycholinguistic characteristics of used stimuli. Comparison of mean psycholinguistic values between nouns and verbs used in the experiment. Data are means ± standard deviations as obtained from the EsPal database.

3.4 Study 4: The right uncinate fasciculus supports verbal short-term memory in aphasia

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Abstract

Verbal short-term memory (STM) deficits are associated with language processing impairments in people with aphasia. Importantly, the integrity of STM can predict word learning ability and anomia therapy gains in aphasia. While the recruitment of perilesional and contralesional homologous brain regions has been proposed as a possible mechanism for aphasia recovery, little is known about the white-matter pathways that support verbal STM in post-stroke aphasia. Here, we investigated the relationships between the language-related white matter tracts and verbal STM ability in aphasia. Nineteen participants with post-stroke chronic aphasia completed a subset of verbal STM subtests of the TALSA battery including nonword repetition (phonological STM), pointing span (lexical-semantic STM without language output) and repetition span tasks (lexical-semantic STM with language output). Using a manual deterministic tractography approach, we investigated the micro- and macrostructural properties of the structural language network. Next, we assessed the relationships between individually extracted tract values and verbal STM scores. We found significant correlations between volume measures of the right Uncinate Fasciculus and all three verbal STM scores, with the association between the right UF volume and nonword repetition being the strongest one. These findings suggest that the integrity of the right UF is associated with phonological and lexical-semantic verbal STM ability in aphasia and highlight the potential compensatory role of right-sided ventral white matter language tracts in supporting verbal STM after aphasia-inducing left hemisphere insult.

1. Introduction

The temporary maintenance of different types of information over the time course of their mental processing and representation is essential for multiple cognitive operations. This includes the input and output processing of linguistic information for effective communication. In aphasia, deficits in language processing at different levels of comprehension and production almost invariably coexist with impaired ability to retain linguistic representations in the short term (Martin, 2000). Therefore, a comprehensive understanding of verbal short-term memory (STM) deficits in aphasia at both the cognitive and neural levels could provide relevant insights into language-based theoretical models of verbal STM and inform aphasia research and clinical practice. To date, several behavioral studies have helped characterize general STM (see Murray, Salis, Martin, & Dralle, 2018 for a review) and specific verbal STM deficits in people with aphasia (PWA) at the phonological and semantic processing levels (see Martin, 2005 for a review). However, only limited research has been conducted to elucidate the brain correlates of verbal STM performance in aphasia. The present study seeks to fill this gap in the literature by characterizing the associations between important white matter tracts and verbal STM performance in aphasia. STM can be thought of as the capacity to store a limited amount of information for a limited time, maintaining it in an active state (Cowan, 2008). However, STM is not a unitary maintenance store and can be viewed as part of working memory (WM), a related construct that emerged to account for different types of temporary memory and to incorporate processing in addition to storage operations (Cowan, 1996, 2008). The most dominant theoretical model in the field was proposed by Baddeley and Hitch (1974). This multi-component model (Baddeley, 2003) entails (i) a limited-capacity central executive control system which seemingly relies on the bilateral frontal cortices (Baddeley & Della Sala, 1996); and two storage systems, (ii) the phonological loop associated with left Brodmann areas 6, 40 and 44 (Baddeley, 2003) and (iii) the visuospatial sketchpad, which appears to be supported by inferior prefrontal, anterior occipital and posterior parietal regions mainly in the right hemisphere (Gathercole, 2008; Papagno, 2018). These two storage systems hold verbal and visual-spatial representations, respectively (see Baddeley, 2003 for a review). In this influential model, the temporary maintenance of language codes is mainly focused on the storage and processing of phonological information (Gupta & Tisdale, 2009).

The phonological loop was put forth as a dual-component system with a phonological store that temporarily holds language memory traces, and a process of articulatory or subvocal rehearsal that keeps this information active and accessible. Support for the phonological loop is based on findings from immediate serial recall tasks showing (i) a phonological similarity effect reflected as shorter memory spans when items are phonologically similar (e.g., similar sounding letters and semantically unrelated but rhyming words) relative to sets with phonologically dissimilar items (Baddeley, 1966; Conrad & Hull, 1964), and (ii) a word-length effect where lists of multisyllabic words are harder to retain compared to single-syllabic word lists (Baddeley, Thomson, & Buchanan, 1975). While the phonological loop has been proposed as a "language learning device" that is crucial to facilitate foreign language acquisition through phonological encoding (Baddeley et al., 1998), Baddeley's model is limited in accounting for the short-term maintenance and processing of semantic information (Baddeley, 1966; Cowan, 2008).

In the last decades, a growing amount of evidence has pointed towards a further division of verbal STM, with the retention of phonological and lexical-semantic information as two separable components (Martin, Schlesinger, Obermeyer, Minkina, & Rosenberg, 2021; Martin, Lesch, & Bartha, 1999; Shivde & Anderson, 2011). Dissociations in verbal STM for phonological and lexical-semantic representations have been described across a variety of case studies presenting with selective STM deficits after brain damage. For instance, Martin, Shelton and Yaffee (1994) demonstrated diverging patterns of verbal STM performance in two patients with acquired brain damage who presented similarly reduced word spans. Specifically, the first patient presenting a large lesion on the left primary auditory cortex, Wernicke's area, and the inferior and superior parietal lobules, showed reduced phonological yet normal semantic effects on word spans. In turn, the second patient, who presented with a lesion on the left posterolateral frontal cortex and the left anterior parietal lobule, showed the reverse pattern of memory performance. Moreover, the first patient also exhibited more impairment on a rhyme probe task assessing phonological STM relative to the second patient, who in turn evidenced better performance on a category probe task tapping lexical-semantic STM. In line with these findings, Majerus and colleagues (2004) described three patients who had recovered from Landau-Kleffner syndrome, a rare

epileptic form of acquired aphasia, but still presented impaired phonological STM on nonword immediate serial recall and rhyme probe tasks, despite normal STM on a lexical-semantic category task. Of note, this dissociation has been corroborated across several studies (see Martin, 2005 for a review). All this evidence argues in favor of considering phonological and lexical-semantic STM as distinct capacities that deserve detailed examination, especially in clinical populations with acquired brain damage.

Importantly, the presentation of isolated verbal STM or language deficits alone is rare. Rather, impairments in both domains are generally found together (Koenigs et al., 2011; Martin & Saffran, 1997; Papagno, Cecchetto, Reati, & Bello, 2007), in particular when lesions involve brain regions essential for sustaining the interaction and communication between language and memory systems (Roger, Banjac, Thiebaut de Schotten, & Baciu, 2022). Indeed, while verbal STM deficits are uncommon in people with left hemisphere damage without aphasia or with right hemisphere damage (Jodzio & Taraszkiewicz, 1999; Kasselimis et al., 2013; Laures-Gore, Marshall, & Verner, 2011), they frequently coexist with language processing deficits in PWA secondary to brain injury (Martin, 2000). There is evidence that phonological and lexical-semantic STM are associated with different aspects of language processing and language learning in this population (see Peñaloza et al., 2022 for a review). For instance, studies on sentence processing in aphasia have shown that phonological STM supports verbatim sentence repetition (Martin et al., 1994; Saffran & Marin, 1975), whereas lexical-semantic STM has been associated with the elaboration of phrases during speech production (Martin & Schnur, 2019; Martin & He, 2004) and the initial retention of word meanings for their integration during verbal comprehension (Martin & He, 2004). Likewise, phonological and lexical-semantic STM have been associated with the ability to learn novel word forms and new word-referent mappings in PWA, respectively (Peñaloza et al., 2015, 2016). Moreover, it has been demonstrated that these two STM components make independent contributions to novel word learning in healthy individuals (Peñaloza et al., 2017) and that the functionality of phonological and lexical-semantic learning abilities in PWA can mirror the integrity of their phonological and lexical-semantic STM (Freedman & Martin, 2001). In addition, the integrity of verbal STM capacity has been associated with response to language treatment

in PWA (Harnish, Schwen Blackett, Zezinka, Lundine, & Pan, 2018) and interventions aiming to improve verbal STM capacity in this population have shown transfer effects to other linguistic abilities including verbal span and narrative discourse in some cases (Martin et al., 2021). Altogether, this evidence highlights the clinical relevance of the examination of verbal STM in PWA given its potential to inform the diagnosis and characterization of language impairment, and its prognostic value on language treatment outcomes. It also underscores the importance of conducting specific and sensitive assessments that measure verbal STM in terms of the type of linguistic information being encoded, whether lexical-semantic or phonological in nature (Martin, Minkina, Kohen, & Kalinyak-Fliszar, 2018), while considering how different language impairment and lesion profiles interact with specific lexical-semantic or phonological STM requirements (Martin & Ayala, 2004).

Although the behavioral research mentioned above has helped to characterize verbal STM abilities in aphasia, the number of studies investigating the neural underpinnings of verbal STM is much more limited. Both neuroimaging studies (Burzynska et al., 2011; Charlton, Barrick, Markus, & Morris, 2013; Henson, Burgess, & Frith, 2000; Paulesu, Frith, & Frackowiak, 1993; Takeuchi et al., 2011) and lesion studies (Baldo & Dronkers, 2006; Basso, Spinnler, Vallar, & Zanobio, 1982; S. Majerus et al., 2004; Meyer, Cunitz, Obleser, & Friederici, 2014; Pisoni et al., 2019; Takayama, Kinomoto, & Nakamura, 2004; Vallar, Basso, & Bottini, 1990; Warrington, Logue, & Pratt, 1971) have consistently pointed to the involvement of left-sided brain regions such as the posterior superior temporal gyrus (pSTG) or the supramarginal gyrus (SMG) and frontoparietal tracts, and more specifically the arcuate fasciculus (AF), as supporting phonological STM. On the other hand, the evidence concerning the neural basis of lexical-semantic verbal STM is even more limited. Various fMRI studies involving healthy subjects suggest that the involvement of the left inferior frontal gyrus (IFG) is important for this ability, as measured by tasks such as synonym judgements (Martin, Wu, Freedman, Jackson, & Lesch, 2003; Shivde & Thompson-Schill, 2004) or semantic anomaly judgements (Hamilton, Martin, & Burton, 2009). Likewise, left IFG lesions appear to be predominantly present in patients presenting with lexical-semantic STM impairments (Hanten & Martin, 2000; Martin et al., 1994; Martin & He, 2004). In a recent study, Martin and colleagues (2021) addressed this question by applying multivariate lesion

symptom mapping (LSM) in 94 acute left-hemisphere stroke patients. Results for phonological WM as measured with the digit matching span task revealed the involvement of cortical regions such as the SMG, the left inferior frontal junction or the postcentral gyrus –possibly related to subvocal rehearsal as a mechanism to avoid the decay of phonological forms prior to providing a matching response (Baddeley, Hitch, & Allen, 2020; Chein, 2001)– as well as subcortical regions including the caudate, the putamen or the lateral prefrontal thalamus. In turn, regions related with lexical-semantic WM as measured by a category probe task included the left IFG, the angular gyrus (AG) and the posterior superior temporal sulcus (pSTS). Although most regions associated with phonological and lexical-semantic WM in the study by Martin et al. (2021) are consistent with previous literature, the proximity –or even partial overlap– of brain regions related to these different verbal STM capacities represent a complicating factor in disentangling their neural underpinnings.

Although maintenance of verbal information appears to be critical for the language system, many models remain vague about the implication and underpinnings of vSTM in language processing. Models focused on language processing (Friederici, 2015; Hickok & Poeppel, 2007; Jacquemot & Scott, 2006) locate verbal STM functions on temporo-parietal areas and their connections with the inferior frontal gyrus. On the other hand, research on verbal STM (Cowan et al., 2011; Martin et al., 1999) proposed that novel phoneme and word serial order might be maintained via a right fronto-parietal network while the maintenance of different verbal stimuli by directing the attentional control would engage the left fronto-parietal network. Finally, integrative models such as the one proposed by Majerus (2013) advocate for combining the elements of the previous two approaches. Despite the differences in the frameworks presented above, they all seem to converge on the idea that the recruitment of dorsal and ventral language networks is critical for verbal STM, which is possibly tapping on mechanisms for the temporary activation of long-term representations of verbal items to be maintained in the language network. Thus, both dorsal and ventral language streams appear to have a prominent role in verbal STM.

Regarding these language streams, the arcuate fasciculus (AF) has been described as the main white matter pathway supporting the dorsal stream, whereas the inferior fronto-occipital (IFOF), the inferior

longitudinal (ILF) and the uncinate (UF) fasciculi are the main white matter tracts related to the ventral stream for language processing (Catani et al., 2005; Dick et al., 2014). Despite the existing evidence supporting the contributions of the abovementioned white matter pathways to phonological and semantic processing, the role of structural connectivity along those tracts in phonological and lexical-semantic STM has not yet been elucidated in aphasia. Considering the high vulnerability of white matter tracts to damage and disconnection following stroke, it is of utmost relevance to assess the white matter structural markers related to the different verbal STM capacities in aphasia.

To this end, the present study aimed to identify the white matter correlates of phonological and lexical-semantic STM in PWA following a left hemisphere stroke. We performed manual deterministic tractography to reconstruct the main language-related white matter tracts bilaterally for each participant and estimated their macro- and microstructural properties by extracting the tract volume and fractional anisotropy (FA) values. All language-related white matter tracts, and especially those with terminations in cortical regions previously associated with verbal STM capacities (Martin et al., 2021) such as the AF, the UF or the IFOF represent good candidates for potentially supporting phonological and lexico-semantic verbal STM in PWA. We further examined the association between these DTI-derived measures and individual scores on phonological and lexical-semantic STM tasks to identify the neural underpinnings of verbal STM in this population, and to gain a better understanding about the white matter tracts that support these abilities after aphasia-inducing brain insults.

2. Material and Methods

2.1 Participants

Participants were 19 chronic stroke patients (5 females, mean age = 60.5 ± 11.13) who were recruited at three local hospitals: Hospital Universitari de Bellvitge (n =16), Hospital de l'Esperança (n = 2), and Hospital Comarcal de l'Alt Penedès (n = 1) (Barcelona province, Spain). All participants were diagnosed with aphasia at hospital admission and continued to present persistent aphasia at the time of study enrolment. One participant (P04) who showed scores within the normal limits across different

language assessments (described in section 2.2) also presented complaints about their everyday language functioning relative to their pre-stroke abilities, indicating that language abilities were not fully recovered. Therefore, the participant was included as impairments in verbal STM measures have been previously reported in people with latent aphasia (Silkes et al., 2021). The following inclusion criteria were employed: (i) age between 25 and 80 years, (ii) Spanish speaker, (iii) right-handed, (iv) unilateral cortical or cortico-subcortical stroke in the left hemisphere confirmed by medical records, (v) at least 6 months post stroke onset, (vi) preserved ability to follow instructions, (vii) eligible for MRI scanning. In addition, none of the participants presented with severe visual or auditory deficits, or a history of psychiatric or neurological disorders other than stroke. Table 1 presents the demographic and clinical information of the stroke participants. All participants provided their written informed consent to undergo study procedures approved by the Institutional Review Board of Hospital Universitari de Bellvitge (reference number: PR224/12) in accordance with the Declaration of Helsinki.

2.2 Language assessment

The diagnosis of aphasia, the evaluation of aphasia severity, as well as the clinical profile of language and speech abilities of the participants were based on the Spanish adaptation of the Boston Diagnostic Aphasia Examination (BDAE-III) (Goodglass et al., 2001). The assessment of language abilities included the following BDAE-III subtests: (i) naming was assessed with the Boston Naming Test (BNT); (ii) repetition was evaluated with the Sentence repetition subtest; (iii) verbal comprehension was determined with the Word comprehension, Commands and the Complex ideational material subtests; and (iv) reading ability was evaluated using the Basic oral word reading and the Oral reading of sentences with comprehension subtests. Aphasia severity was determined using the BDAE Severity scale and the BDAE Language Competency Index which summarizes each participant's scores on the main production and comprehension subtests. Finally, verbal comprehension was further assessed with the Token Test (De Renzi & Faglioni, 1978) and verbal fluency was evaluated with semantic fluency (animals) and letter fluency tasks (words beginning with the letter P) (Pena-Casanova et al., 2009).

Table 2 presents the individual participants' scores across all language assessments reported in this section.

2.3 Assessment of phonological processing and verbal STM

A selection of subtests from the Temple Assessment of Language and Short-Term Memory in Aphasia (TALSA; Martin et al., 2018) available in Spanish were administered to all participants to evaluate phonological processing and verbal STM, and composite scores were computed as done in previous aphasia studies (Peñaloza et al., 2017, 2016). Table 3 reports the scores of each participant on the described tests.

2.3.1 Phonological processing

Two TALSA subtests were administered to evaluate phonological processing. The rhyming judgments subtest required participants to decide whether pairs of words and nonwords presented auditorily rhymed or not. The phoneme discrimination subtest assessed the ability to discriminate if pairs of words and nonwords presented auditorily were the same or not. Each of these subtests was administered under two conditions with variations in memory load. The 1-second unfilled interval condition presented the words and nonwords of each pair separated by a 1 second delay, whereas the 5-second unfilled interval condition included a 5-second delay between the first and second stimulus of each word and nonword pair. Each condition in the rhyming judgments and the phoneme discrimination subtests included 20 words and 20 nonword pairs. Accuracy across conditions and tasks were summed up into a final phonological processing composite score for each participant.

2.3.2 Verbal STM

A set of TALSA subtests including verbal STM measures, either non-lexical (nonword repetition) or lexical (word repetition span, digit repetition span, word pointing span, digit pointing span), were administered to assess different aspects of verbal STM. The nonword repetition subtest assessed the

ability to repeat 15 nonwords of 1, 2 or 3 syllables, created by altering one or two phonemes in real words. This subtest included two conditions that required the repetition of nonwords either after a 1-second or a 5-second interval as a way of manipulating STM load. A nonword repetition composite score was calculated by computing the percentage of correct responses in each interval condition and averaging these values across conditions. This composite score represents a measure of *phonological STM with speech output* as stimuli represented phonotactically legal "words" with no lexical-semantic representations. The word and digit repetition span tasks required participants to listen to a sequence of words or digits and repeat them immediately after its presentation, in the same order. The word and digit pointing span tasks required the participants to listen to sequences of words or digits and reproduce them in the same order by pointing at their corresponding pictures on a visual array of 9 possible items (the position of the items within the array was randomized across trials). Each repetition and pointing span task presented 10 strings of stimuli (words or digits) in each of 7 string lengths (1 item, 2 items, 3 items, etc.). In all cases, words and digit names were matched in syllable length, and sequences were generated from a finite set of 9 items, avoiding repetitions within the sequences. The final span size achieved in each task was calculated using the formula: string length at which at least 50% of the strings are recalled + (.50 x proportion of strings recalled in the next string length), as suggested in previous research (Shelton, Martin, & Yaffee, 1992). The computed spans were then used to calculate two final composite spans: the repetition composite span which averaged the word and digit repetition spans and served as a measure of *lexical-semantic STM with speech output*; and the pointing composite span which averaged the word and digit pointing spans and tapped into *lexical-semantic STM without speech output*. It is worth noting that while the first measure requires the phonological route for repetition and speech output, the second measure can be considered a purer measure of lexical-semantic STM as it does not require speech output (Peñaloza et al., 2016). These three composite verbal STM scores representing *phonological STM with speech output, lexical-semantic STM with and without speech output* were the behavioral variables of interest for this study.

Table 1 Demographic and clinical information of the participants

Participants	Sex	Age (years)	Education (years)	TPO (months)	Aphasia type	Aphasia severity rating (1–5)	Aetiology	Lesion location (Left Hemisphere)	Lesion volume (cc)
P01	M	78	4	25	Global	1	Ischemic	Frontal regions, including IFG, MFG and SFG as well as the precentral and postcentral gyri and the rolandic operculum, temporal regions like STG and the ATL, the insula and the putamen	72, 93
P02	M	58	12	40	Transcortical motor	3	Ischemic	Parietal regions (postcentral gyrus and superior and IPL), frontal regions, including IFG, MFG, SFG and the precentral gyrus, the rolandic operculum and the insula	92, 71
P03	M	61	18	26	Anomic	4	Ischemic	Frontal regions, including IFG, MFG and SFG as well as the precentral and postcentral gyri, the STG, the insula and the lentiform nucleus	47, 23
P04	M	62	11	24	Recovered	WNL	Ischemic	The temporal lobe, primarily the MTG and, to a lesser extent, the ITG and STG	9, 20
P05	M	51	5	20	Fluent	3	Ischemic	Mainly the left temporal lobe (STG and MTG) but also parts of the parietal (IPL and precuneus) and occipital lobes	7, 59
P06	F	75	6	20	Fluent	5	Ischemic	The insula, the lentiform nucleus and a portion of the IFG	5, 42
P07	M	63	8	41	Fluent	4	Ischemic	The frontal lobe -primarily the IFG and, to a lesser extent, the MFG- and the Insula	17, 26
P08	F	40	12	14	Broca's	2	Ischemic	The Parietal lobe (IPL and Postcentral gyrus), Temporal regions (STG and MTG), the insula and the lentiform nucleus	33, 70
P09	M	47	8	6	Broca's	3	Ischemic	The temporal lobe (STG, MTG, the TTG and the ATL), frontal regions (IFG and the precentral Gyrus) the postcentral gyrus and the insula	31, 29
P10	M	42	14	11	Mixed Nonfluent	1	Ischemic	The entire frontal and parietal lobes, some temporal regions like the STG, the TTG and the ATL, the insula, the lentiform nucleus and the para- and hippocampal regions	186, 40
P11	M	51	13	33	Fluent	5	Ischemic	Mainly the temporal lobe (STG, MTG, ITL and ATL) but also the IFG and the insula	15, 50
P12	M	69	8	24	Fluent	5	Ischemic	Mostly the parietal Lobe (SPL, IPL, postcentral gyrus) and, to a lesser extent, frontal (IFG, MFG, the precentral Gyrus) and temporal (STG, MTG, TTG) regions and the insula	63, 68
P13	M	61	11	34	Fluent	5	Ischemic	The temporal lobe (STG and MTG), the IPL and the insula	5, 63
P14	F	72	6	38	Fluent	5	Ischemic	A part of the lentiform nucleus and the insula	0, 48

Table 1 (continued)

Participants	Sex	Age (years)	Education (years)	TPO (months)	Aphasia type	Aphasia severity rating (1–5)	Aetiology	Lesion location (Left Hemisphere)	Lesion volume (cc)
P15	F	57	8	9	Nonfluent	3	Ischemic	The frontal lobe (IFG, MFG and precentral gyrus), the postcentral gyrus and the rolandic operculum, the STG and the insula	9, 67
P16	F	71	6	18	Mixed – Nonfluent	2	Undetermined	The frontal lobe (Precentral Gyrus and parts of IFG, MTG and SFG) and also the rolandic operculum, the postcentral gyrus, the IPL, the STG, the lentiform nucleus and the insula	44, 74
P17	M	58	5	36	Broca's	2	Undetermined	The frontal lobe (precentral gyrus, IFG, MTG), the rolandic operculum, the STG and the insula	23, 18
P18	M	52	11	41	Transcortical motor	3	Ischemic	The frontal lobe (precentral gyrus and parts of the IFG, MTG ad SFG), the rolandic operculum, postcentral gyrus, the STG and the insula	32, 58
P19	M	73	14	31	Fluent	3	Ischemic	Most of the frontal lobe (IFG, MFG, precentral gyrus), parietal regions (IPL and postcentral gyrus), the rolandic operculum, some temporal parts (STG, MTG, ATL), the putamen, the middle occipital lobule, and the insula	77, 89

Demographic and clinical information for each participant. All the lesions described were strictly left-sided

TPO time post-stroke, *CC* cubic centimeters, *M* male, *F* female, *WNL* within normal limits, *IFG* inferior frontal gyrus, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *ITG* inferior temporal gyrus, *MTG* middle temporal gyrus, *STG* superior temporal gyrus, *TTG* transverse temporal gyrus, *ATL* anterior temporal lobe, *IPL* inferior parietal lobule, *SPL* superior parietal lobule

Table 2 General language evaluation scores of the participants

Participant	BDAE-III									Token Test (36 max)	Animal Fluency	Letter Fluency
	Language Competence Index (100 max)	Word Reading (30 max)	Sentence Reading (10 max)	Comprehension in Reading (5 max)	BNT (60 max)	Sentence Repetition (10 max)	Word Comprehension (37 max)	Commands (15 max)	Complex Ideational material (12 max)			
P01	24.16	**6**	NA	NA	**22**	**3**	**26**	**11**	**8**	**14**	**0**	**1**
P02	71.67	30	8	**4**	51	9	37	15	10	**31.5**	**12**	**3**
P03	90	30	10	5	**41**	10	37	15	12	35.5	**13**	**4**
P04	97.5	30	10	5	57	9	37	15	12	34.5	25	9
P05	46.65	30	9	**3**	**42**	9	**29**	**11**	**4**	**28**	**13**	**7**
P06	91.65	30	10	5	50	10	37	15	10	34	10	**4**
P07	79.15	30	10	5	53	9	36.5	15	11	31.5	**12**	**6**
P08	55.8	**23**	**2**	5	**38**	**4**	37	14	10	**20**	**6**	**5**
P09	71.65	30	8	5	48	7	37	15	10	34.5	**13**	**2**
P10	40.83	**20**	**1**	**3**	**41**	**2**	**32**	**11**	10	**12.5**	**4**	**1**
P11	95.85	30	10	5	58	8	37	15	11	35	**16**	**9**
P12	87.5	29	8	**4**	49	9	37	15	10	**28**	22	9
P13	83.33	30	10	5	51	10	36	14	12	32.5	**14**	10
P14	89.16	30	10	5	55	9	35	15	12	32	24	12
P15	60.835	**27**	10	**3**	46	8	**34**	15	**5**	**29.5**	**6**	**3**
P16	47.5	NA	NA	NA	**39**	9	34.5	13	**7**	**19.5**	**5**	**3**
P17	49.16	**27**	7	5	**41**	**4**	**32**	15	**4**	**25.5**	**7**	**4**
P18	64.16	30	10	5	53	9	37	14	**6**	**28**	**13**	**5**
P19	49.16	30	6	**2**	**22**	8	**34**	**10**	**4**	**21**	**4**	**4**

Bold numbers indicate scores that fall below the normal limits according to healthy participant normative data. Scores on the BDAE-III below the 50th percentile according to normative data from PWA considered for the development of this diagnostic battery are marked in bold

BDAE-III Boston Diagnostic Aphasia Examination-Third Edition, *BNT* Boston Naming Test, *NA* not available

Participant	Phonological Composite Score	Verbal STM		
		NW Repetition	Pointing Span	Repetition Span
P01	0,6875	0,166	1,5	1,9
P02	0,9875	0,566	3,8	3,8
P03	1	0,6665	4,5	5
P04	1	0,865	5,7	6,2
P05	0,875	0,433	2,9	2,8
P06	1	0,53	3,8	3,6
P07	0,975	0,633	4,8	4,8
P08	0,975	0,3665	2,8	3,3
P09	0,975	0,466	4,2	4,7
P10	0,975	0,2995	2,2	1
P11	1	0,765	4,7	5,1
P12	0,9875	0,233	4,8	4,7
P13	1	0,735	5,4	5,6
P14	0,975	0,8	4,7	5
P15	0,8	0,3995	3,2	3
P16	0,75	0,433	3,2	4
P17	0,925	0,6665	3,1	3,6
P18	1	0,7995	4,4	4,5
P19	0,9375	0,565	3,8	3,3

Table 3 – Phonological processing and verbal STM composite score for each patient. Abbreviations: verbal STM = verbal Short-Term Memory; NW = Nonword.

2.4 Neuroimaging data

2.4.1 MRI acquisition

All participants were scanned on a Siemens Magnetom 3T scanner with the Syngo MR B17 software and using a 32-channel head coil at Hospital Clinic, Barcelona (Spain). Diffusion-weighted images (DWI) were acquired with a spin-echo echo-planar imaging (EPI) sequence [TR = 5100 ms; TE = 80 ms; 48 axial slices; 64 directions, GRAPPA (generalized autocalibrating partially parallel acquisitions) acceleration factor 4; slice thickness = 2.5 mm; FOV = 23.5 cm; acquisition matrix = 94 x 94; voxel size = 2.5 mm^3] with one non-diffusion (b = 0 s/mm2) and 64 diffusion weighted volumes (b = 1000 s/mm2). A high-resolution T1 (MPRAGE) image was also acquired in the same session (TR = 1970 ms; TE = 2.34 ms; slice thickness = 1.0 mm; acquisition matrix = 256 x 256; voxel size = 1.0 x 0.8 x 0.4 mm).

2.4.2 MRI preprocessing

Prior to preprocessing, all images were visually inspected to ensure the absence of any major artifact that could not be corrected in subsequent steps. Lesions were manually traced slice-by-slice for each participant on their T1 structural brain images by GO using the MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron) and were further verified by an experienced neurologist (see Figure 1 for the lesion overlay map across participants). Next, as the first step in the preprocessing, T1-weighted images were warped and adjusted to the Montreal Neurological Institute (MNI) space using the Statistical Parameter Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, www.fil.ion.ucl.ac.uk/spm/). The warps obtained were then used to normalize the lesion masks to MNI space. MRIcron was again employed to extract individual total lesion volumes and the xjview toolbox (https://www.alivelearn.net/xjview) was used to identify anatomical structures affected by stroke in each participant (Table 1).

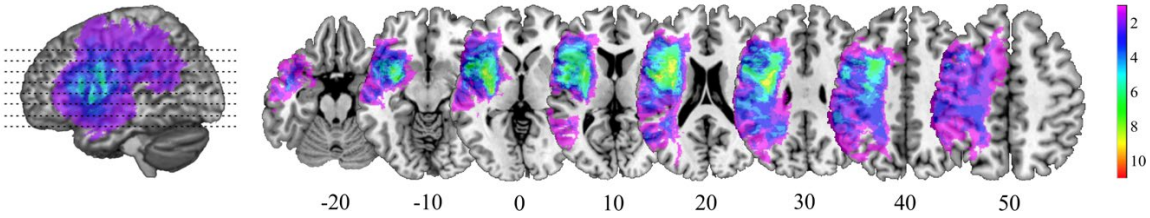

Figure 1 – Lesion overlay map

Lesion overlay maps based on lesion masks delineated on T1-weighted images. Montreal Neurological Institute space coordinates of the structural template slices are specified at the bottom of the image and represented by dotted lines on the rendering in the right side of the figure. Figure adapted from Olivé et al., 2023.

All diffusion images were pre-processed using the FMRIB Software Library (FSL www.fmrib.ox.ac.uk/fsl/fdt) and the Diffusion Toolkit software (DTK) (Wang et al., 2015). DWI data were processed as in previous studies from our team (Olivé et al., 2022; Vaquero et al., 2021) following these steps: (i) eddy-current correction using the FMRIB Diffusion Toolbox (FDT), part of FMRIB Software Library (FSL www.fmrib.ox.ac.uk/fsl/fdt); (ii) brain extraction using FSL Brain Extractor Tool (Smith, 2002, 2004; Woolrich et al., 2009) with 0.3 as threshold value; (iii) rotation of the b-vectors; (iv) reconstruction of the diffusion tensors using DTK (Wang et al.,

2015); and (v) whole-brain deterministic tractography using DTK with 35 degrees as maximum curvature and a minimum FA threshold of 0.2.

2.4.3 Tract dissections

Manual deterministic tractography was performed on preprocessed images focusing on four main language-related white matter tracts: the three segments of the arcuate (AF), inferior fronto-occipital (IFOF), inferior longitudinal (ILF), and uncinate (UF) fasciculi. These tracts were dissected bilaterally for each patient in native space using the Trackvis software (v.0.6.0.1, http://trackvis.org/) by manually placing Regions of Interest (ROI) as described in previous research (Catani & Thiebaut de Schotten, 2008; see Olivé et al., 2022 for ROI placement examples of the tracts dissected here).

AF. The three segments of the AF were dissected using a three-ROI approach, each drawn in a single slice as described in previous studies (Catani et al., 2005; Lopez-Barroso et al., 2013). The first ROI was delineated in the coronal plane encompassing the fibers going to the IFG, including BA44 and 45 (frontal); the second ROI was drawn in the axial plane covering the white matter fibers traveling to the superior temporal gyrus (temporal); and the third ROI was depicted on the sagittal view, covering the supramarginal and angular gyri (parietal). These ROIs were combined to reconstruct the three subdivisions of the AF: the long (fronto-temporal), the anterior (fronto-parietal), and the posterior (temporo-parietal) segments.

ILF, UF and IFOF. To delineate these three white matter pathways supporting the ventral stream for language processing (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009), we combined three ROIs according to previous studies (Catani & Thiebaut de Schotten, 2008). The first ROI was placed axially at the level of the anterior temporal lobe (temporal ROI) encompassing an average of 5 slices; the second one on the anterior floor of the external/extreme capsule covering an average of 3 slices (frontal ROI); and the third one on the region located between the occipital and temporal lobes covering an average of 7 slices (occipital ROI). To define the tracts of interest, we applied a two-ROI approach: the ILF was comprised by fibers

going through the temporal and occipital ROIs; fibers going through both temporal and frontal ROIs were part of the UF; and the fibers crossing the frontal and occipital ROIs formed the IFOF.

Additionally, exclusion ROIs were used for each of the tracts in order to remove any artefactual fibers when present, as commonly done in manual reconstructions (Elmer et al., 2019; Vaquero et al., 2021). For visualization purposes, the streamlines were rendered using the "tube" render option of TrackVis with a radius of 0.15 mm and 10 sides. A depiction of dissections for all participants is provided in Figure 2.

Output measures extracted from every tract and hemisphere included macrostructural (volume) and microstructural (Fractional Anisotropy, FA) values. Tract volumes are thought to reflect the number of times a streamline could be reconstructed between two brain regions (D. K. Jones et al., 2013). Although this measure does not indicate the real fiber count of the tract (Jones et al., 2013), it has been used as a proxy of the tracts' macrostructure in several DTI studies (Catani et al., 2007; Olivé et al., 2022; Wan et al., 2012) and it is thought to be modulated by properties of the tract including fiber-packing or myelination (Vaquero et al., 2021). As for microstructure, our DTI marker of interest was fractional anisotropy (FA). It reflects the degree of anisotropy (Winston, 2012) and numerous intrinsic characteristics including fiber count and dispersion, packing density, myelination or membrane permeability. FA has also been widely used in the DTI literature (Lebel & Beaulieu, 2009; Molinuevo et al., 2014) and, together with tract volume, it is considered to be a sensitive measure to explore individual differences (Vaquero et al., 2017). Furthermore, these measures are not only useful for studying healthy anatomy; they also provide valuable information about brain structural connectivity characteristics after a stroke or brain tumor (François et al., 2019; Simó et al., 2015), and have been previously used for investigations in PWA (Forkel & Catani, 2018; Ivanova et al., 2016; Schlaug, Marchina, & Norton, 2009; Yang et al., 2017).

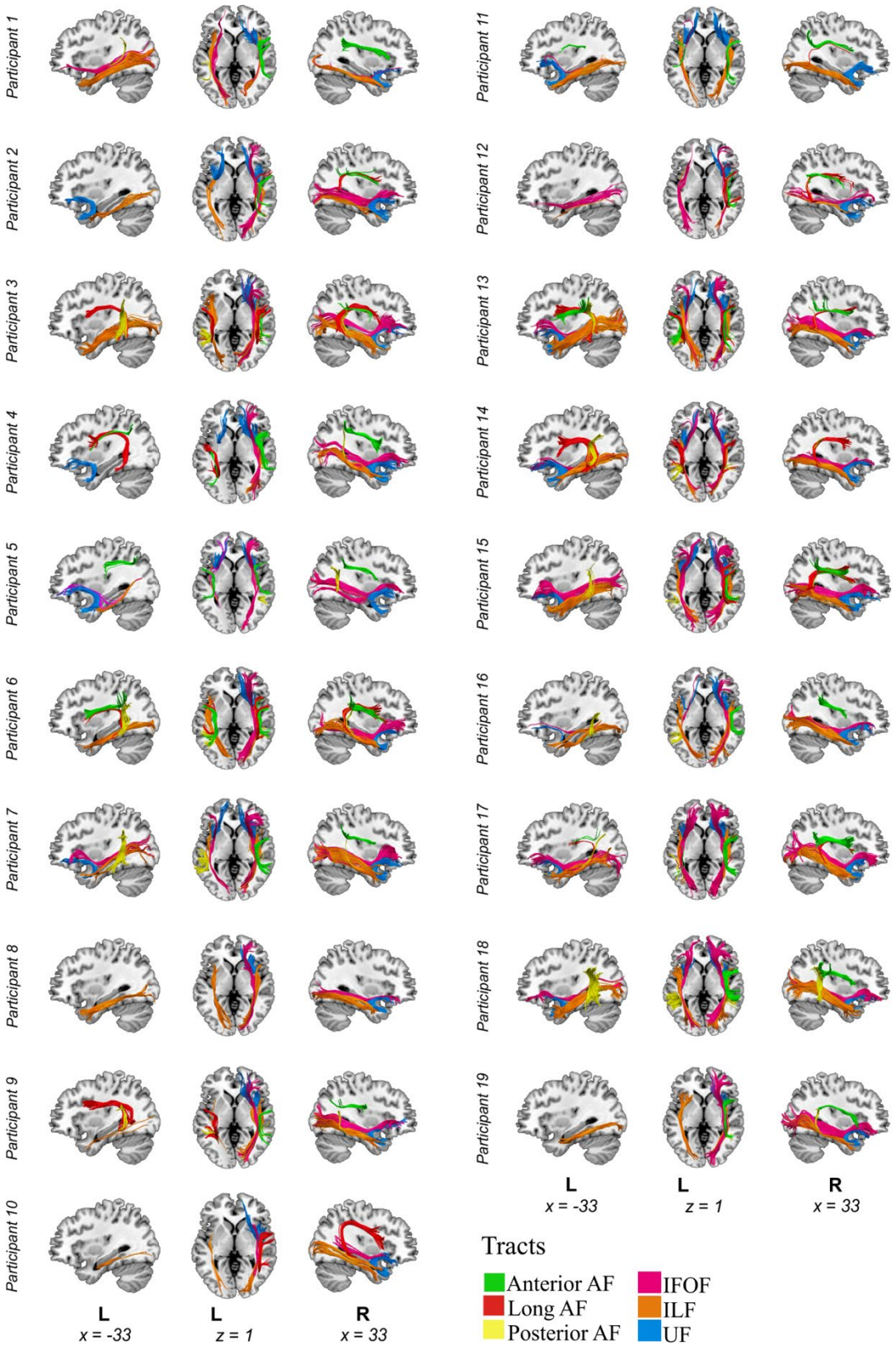

Figure 2 – Dissections of all participants. Manual deterministic tractography reconstructions from all participants. Tracts reconstructed were the three segments of the arcuate fasciculus (AF) [Green = anterior, red = long, yellow = posterior segments], Inferior Fronto–Occipital Fasciculus (IFOF) [Magenta], Inferior Longitudinal Fasciculus (ILF) [Orange] and Uncinate Fasciculus (UF) [Light blue]. Abbreviations: L, left. Montreal Neurological Institute space coordinates of the structural template slices are specified at the bottom of the image. Figure adapted from Olivé et al., 2023.

2.5 Statistical analyses

Statistical analyses were conducted using the IBM SPSS software (v25.0). To assess the relationships between white matter macro- and microstructural organization and verbal STM performance in PWA, Pearson correlations were calculated to examine associations between measures of phonological and lexical-semantic STM (nonword repetition, pointing span, and repetition span composite scores) and both mean volume and FA values extracted for each tract and hemisphere. Of note, specific tracts could not be reconstructed for some participants (see Supplementary Table 1 for details on missing tracts per hemisphere). In such cases, volume was computed as zero, whereas FA was removed from the correlation analyses.

The False Discovery Rate (FDR) correction was used to adjust for multiple comparisons and all p values are reported after this correction. FDR corrections were performed separately for each tract and white-matter related measure (6 correlations per tract and measure: 2 hemispheres x 3 verbal STM scores). Additionally, an FDR correction was performed for volume and FA separately with all tracts (32 correlations per measure: 6 tracts/segments x 2 hemispheres x 3 verbal STM scores).

Overall lesion volume was significantly correlated with nonword repetition ($r = -0.498$, $p = .03$), repetition span ($r = -0.626$, $p = .004$) and pointing span ($r = -0.480$, $p = .038$) composite scores. Likewise, aphasia severity (as measured by the BDAE Language Competence Index) was significantly correlated with all three measures: nonword repetition ($r = 0.615$, $p = .005$), repetition span ($r = 0.827$, $p < .001$) and pointing span ($r = 0.883$, $p < .001$) composite scores. Thus, we further examined the contributions of overall lesion volume and aphasia severity to any relationships between white matter measures and verbal STM scores, FDR-corrected significant correlations were reanalyzed as partial correlations using normalized total lesion volume and the BDAE Language Competence Index as control covariates. Of note, the BDAE Language Competence Index was preferred over the traditional BDAE aphasia severity scale for this analysis because it captures a larger individual variability in terms of overall language impairment (range 0 – 100 percentile scores) while accounting similarly for both comprehension and

expression abilities. The BDAE aphasia severity rating scale allows one to classify severity only on a limited 5-point scale which is largely determined by fluency in language production relative to verbal comprehension (Goodglass et al., 2001).

Given the extensive lesions presented by some of the participants, which prevented us from reconstructing some of their left hemisphere tracts, any significant relationship could be influenced by the disconnection caused by the lesion rather than by the overall lesion volume itself. To account for this possibility, we performed a track-wise lesion analysis using Tractotron as implemented in the BCBtoolkit (http://toolkit.bcblab.com/). This method individually compares the lesion mask of every subject to an atlas of the white matter tracts in the healthy adult brain to provide two parameters for each tract: (i) the probability that the lesion intersects a given tract, and (ii) the possible proportion of disconnection of that same tract. Therefore, we extracted these two values for all the left hemisphere tracts and used them as covariates to reanalyze any FDR-corrected significant correlations. On the other hand, other participants (n = 5) presented smaller lesions (< 10 cc) compared to the rest of the sample. To ensure that these less affected individuals did not make an overly large contribution to any possible associations between verbal STM scores and white-matter metrics, all significant FDR-corrected associations were further analyzed excluding these participants.

3. Results

3.1 White matter tract volume and verbal STM

The right UF emerged as the main white matter tract involved in verbal STM in our cohort of PWA, with tract volume showing significant correlations with all three measures of verbal STM (FDR corrected). Specifically, the right UF volume was significantly correlated with nonword repetition ($r = 0.680$, $p = .006$), pointing span ($r = 0.523$, $p = .044$), and repetition span ($r = 0.560$, $p = .039$) composite scores after the FDR correction was performed independently for every tract (number of comparisons: 6). Figure 3 provides a depiction of these significant associations. Importantly, only the correlation between the right UF volume and nonword repetition scores (r

= 0.680, p = .036) survived FDR corrections for the multiple comparisons performed for all tracts and hemispheres (number of comparisons: 36). Similarly, partial correlations controlling for both lesion volume and aphasia severity as measured by the BDAE Language Competence Index corroborated this significant association between the right UF volume and nonword repetition scores (r = 0.595, p = .012) although its correlations with pointing span (r = 0.426, p = .088), and repetition span (r = 0.451, p = .069) scores became statistically non-significant.

The results of all the reanalysis using the probability and proportion of tract disconnection as a covariate can be found in Supplementary Table 2. When controlling for the proportion and probability of disconnection of the left UF, the above-mentioned FDR-corrected significant correlations remained significant. These partial correlations also remained significant when using as covariates the probability of disconnection of all the left hemisphere tracts dissected. However, when using the proportion of disconnection of all the dissected left hemisphere tracts as covariates, only the association between the volume of the right UF and nonword repetition remained significant (r= 0.578, p=.039), while the associations with repetition (r=0.477, p=.100) and pointing scores (r=0.407, p=.168) became statistically non-significant. Finally, very similar results were obtained when excluding the data of the 5 less affected individuals. Specifically, the analysis with the remaining 14 participants showed a significant correlation between the right UF volume and nonword repetition composite scores (r=0.712, p=.004) while the correlations between the right UF volume and both repetition (r=0.361, p=.204) and pointing (r=0.388, p=.170) composite scores became statistically non-significant.

Additional associations between white matter volume and verbal STM scores were statistically significant, albeit none of them survived FDR correction. Uncorrected significant correlations at the .05 level are depicted in Supplementary Figure 1.

3.2 White matter tract FA values and verbal STM

FA values were not significantly correlated with any of the verbal STM measures for any of the tracts / hemispheres in the present sample ($p \geq 0.05$ in all cases). The results from all correlations performed for volume and FA measures are shown in Supplementary Tables 3 and 4, respectively.

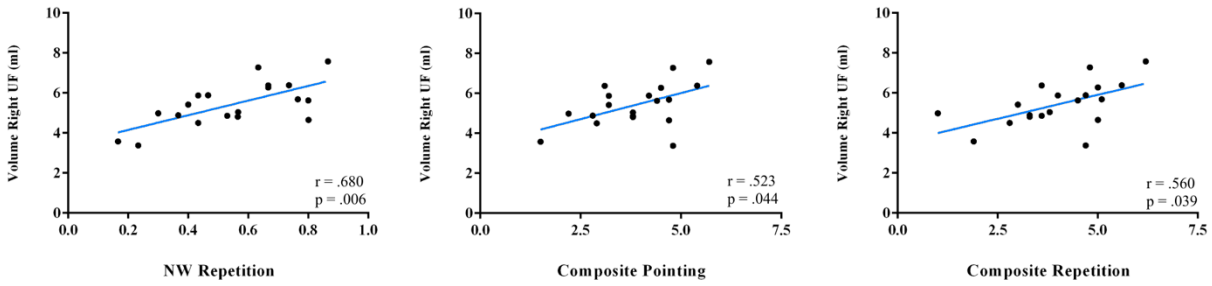

Figure 3 – Significant FDR corrected correlation results. Statistically Significant Pearson correlations after FDR correction performed independently for every tract. *P*-values in the figure are already FDR-corrected (6 comparisons). Figure adapted from Olivé et al., 2023.

4. Discussion

The aim of this study was to investigate the white matter structural correlates of phonological and lexical-semantic STM in post-stroke chronic aphasia. Manual deterministic tractography was used to reconstruct the main language-related white matter pathways in the brain including the AF, UF, IFOF, and the ILF. White matter tract volume and FA values were extracted bilaterally for each tract and their relationships with phonological and lexical-semantic STM composite scores were evaluated before and after partialling out the effects of aphasia severity and overall lesion volume. We found that white matter tract volumes, but not FA values, were associated with verbal STM in PWA, suggesting that macro-structural properties of white matter fibers are more sensitive to capture individual differences in verbal STM performance in chronic aphasia. In particular, we found a strong association between the right UF volume and all measures of phonological and lexical-semantic STM. Among these, the strongest association was found between the right UF volume and nonword repetition composite scores after controlling for overall lesion volume, aphasia severity, the disconnection of left hemisphere tracts and the

potential contribution of the cases presenting with the smallest lesions in the sample. This result strongly points to a role of the right UF in phonological verbal STM in chronic aphasia.

It is worth considering these findings in light of current neurocognitive models of language processing and verbal STM. Based on the functional specialization of the dorsal and ventral pathways for language processing proposed by these models (Friederici, 2015; Hickok & Poeppel, 2007; Jacquemot & Scott, 2006), one would expect an association between dorsal white matter tracts and nonword repetition composite scores reflecting phonological STM on one hand, and between ventral pathways and repetition and pointing composite spans reflecting lexical-semantic STM on the other. Further, when considering hemispheric lateralization, one would also expect that phonological STM would rely on left lateralized white matter tracts as the dorsal stream for phonological processing is assumed to be strongly left–hemisphere dominant, and that lexical-semantic STM would be supported by ventral tracts in both hemispheres as the ventral stream for semantic processing should be bilaterally organized in neurotypical individuals (Bajada et al., 2015; Hickok & Poeppel, 2007). Given these considerations of functional and hemispheric / neuroanatomical specialization, the expectations mentioned above would be particularly relevant to patients examined in the acute/subacute phase after stroke as the functionality of verbal STM (as any other cognitive ability) at this phase would be predominantly reflective of neural integrity (Martin et al., 2021). Nonetheless, our sample exclusively included participants with chronic aphasia, who may have developed specific STM strategies to compensate for their language and verbal STM dysfunction resulting from stroke. Thus, the associations between verbal STM components and the specific white matter tracts and their hemispheric lateralization in this patient sample may reflect some degree of post-stroke functional reorganization. With this consideration in mind, our findings were partially aligned with the above-described expectations in that the volume of the right UF was significantly correlated with both measures of lexical-semantic STM (FDR corrected). This finding supports the classical functional division of the dorsal and ventral streams and suggests that the right UF may still support verbal STM for lexical-semantic representations even after damage to the left UF tract and/or its cortical terminations. This interpretation aligns with the possibility of right hemisphere

compensation which may capitalize on the bilateral organization of the ventral stream for semantic processing (Bajada et al., 2015; Hickok & Poeppel, 2007).

However, not all correlations between dorsal and ventral white matter tracts and verbal STM measures were in line with the potential associations expected according to models of the dorsal and ventral pathways (Dick & Tremblay, 2012; Hickok & Poeppel, 2007). Indeed, the volume of the right UF, a ventral white matter pathway, was associated with phonological STM, which would be presumably supported by the dorsal stream. One possible interpretation of these results is that this dorsal-phonological versus ventral-semantic dichotomy may not be as clear as previously proposed, at least in terms of their contributions to different components of verbal STM. Even though phonological processing has repeatedly been associated to the left dorsal stream, some studies have postulated the role of right hemisphere structures, namely frontoparietal tracts, on some aspects of verbal STM such as novel phoneme maintenance and especially word serial order information (Majerus, 2013). This would go in line with our results since the strongest association found was precisely between nonword repetition and volume of a right hemisphere structure, in this case the right UF. The invalidation of this clear dorsal-phonological-ventral-semantic dichotomy in relation to the verbal STM would also make sense from an anatomical point of view, given the proximity –or even partial overlap– of the cortical regions that have been previously associated with phonological and lexical-semantic STM (Martin et al., 2021). Moreover, different white matter tracts of either the dorsal or ventral streams of language processing, have terminations in these regions and could constitute structural support for verbal STM abilities. More specifically, the UF is a long-range white matter tract connecting temporal regions including the anterior temporal lobe (ATL), the uncus and entorhinal and perirhinal cortices with the orbitofrontal and lateral prefrontal cortices, the frontal pole and the anterior cingulate gyrus (Dick et al., 2014; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012; Von Der Heide et al., 2013). Therefore, the UF presents terminations in inferior frontal regions, which have been associated with both phonological (Chein, 2001; Yue, Martin,

Hamilton, & Rose, 2019) and lexical-semantic verbal STM (Lewis-Peacock, Drysdale, Oberauer, & Postle, 2012; Martin et al., 2003; Shivde & Thompson-Schill, 2004).

Although its role is still debated (Papagno et al., 2011), the UF is considered as part of the ventral stream of language processing (Hickok & Poeppel, 2007), thought to support the mapping of sound-based speech representations to distributed conceptual representations (Saur et al., 2008). Two of the functions most ascribed to this tract are naming and lexical-semantic processing, which have also been attributed to the ATL (Dick & Tremblay, 2012; Papagno et al., 2011). Although it has received less attention beyond its role in language, the UF has also been linked to memory functions since it connects the ATL, believed to contribute to semantic memory, and the entorhinal cortex that is related to episodic memory functions carried out in the hippocampus (Von der Heide et al., 2013). Moreover, microstructural properties of the UF have been associated with working memory in normal aging (Charlton, Barrick, Lawes, Markus, & Morris, 2010) and even to auditory-verbal declarative memory measures in both children (recall measures of word list learning; Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Schaeffer et al., 2014), and in adults with temporal lobe epilepsy (immediate and delayed auditory memory; Diehl et al., 2008; McDonald et al., 2008), as well as to lexical-semantic learning in healthy young adults (Ripollés et al., 2017). The previously mentioned links between the UF and memory functions support the potential role of this white matter tract in verbal STM. It should be noted that these previous associations have been found between memory functions and white-matter microstructural parameters such as FA, but not with tract volume. However, most of these studies simply did not include tract volume as a variable in their research. Moreover, as previously discussed, FA can reflect various subcellular processes (Winston, 2012) and some changes in fiber microstructure may not be reflected in the average FA value even if they have occurred. In addition, the fact that FA is a summary parameter implies that changes in various diffusion directions may remain uncovered (Aung et al., 2013). Thus, the interpretation of the neural correlates of FA values in our study must be done carefully, and it is important to keep in mind

that several factors could account for our lack of significant findings concerning the relationship between UF's microstructure and verbal STM performance.

Notably, while there is a growing number of DTI studies mapping a variety of cognitive functions to specific white matter tracts, the presence of mixed findings and the lower number of studies addressing some white matter tracts relative to others, make it difficult to assign one or more functions to a specific white matter tract. One of the reasons contributing to this difficulty is that the terminations of any given tract can be –and usually are– also connected to other tracts, such that they can form a network of connections with several parallel pathways between two given regions of the brain. The fact that alternative pathways could communicate particular brain regions involved in different aspects of verbal STM (such as the inferior frontal regions) also allows considering that the associations between STM and white matter tracts found in the current study might reflect adaptation processes following stroke. Indeed, brain plasticity mechanisms could account for the possibility that white matter tracts not intrinsically related phonological or lexical-semantic STM could assume these functions following acquired brain injury. For instance, Duffau and colleagues (2009) argued that the UF is not systematically essential for language, as other tracts of the semantic ventral stream (such as the IFOF) can compensate for it in case of functional alterations. Similarly, previous descriptions have stated that the connection between the posterior superior temporal sulcus (pSTS) and the IFG –at both functional and structural levels– can be supported in alternative ways in addition to the direct physical link provided by the AF (Catani et al., 2005; Friederici, 2015), including the UF. This possibility is further supported by studies showing that dorsal and ventral pathways can compensate each other and carry out functions typically ascribed to the other language stream under high demand or functional constraints (Lopez-Barroso et al., 2011; Yeatman, Dougherty, Ben-Shachar, et al., 2012) and after brain damage (Rauschecker et al., 2009; Torres-Prioris et al., 2019). In addition, the fact that a right hemisphere tract correlated with phonological STM measures relying on a predominantly left-lateralized dorsal stream, is in line with multiple sources of evidence showing right hemispheric recruitment reflecting compensatory changes in the contralesional hemisphere in

PWA following a left hemispheric stroke (see Kiran & Thompson, 2019 for a review). In fact, Schneider et al. (2022) recently studied the effect of left-hemispheric stroke lesion location and time post stroke on right hemisphere language activation. Their results revealed that lesions to the left extreme capsule –the anatomical location through which the UF passes through on its fronto-temporal trajectory– are associated with an increased acute to chronic right-hemisphere activation. In turn, the activity of some of these right-hemisphere regions (SMA and IFG) is associated with increased language comprehension performance (Schneider et al., 2022).

To this point, one of the questions that remains open is whether the involvement of the right-hemisphere white matter tracts –especially the UF– in different aspects of verbal STM is intrinsic to these cognitive processes or whether it only occurs as an adaptive strategy to compensate for the lesions observed in the left hemisphere. The premorbid status and volume of right hemisphere tracts might be an important factor defining whether the contralesional hemisphere engages in post-stroke recovery (Kiran & Thompson, 2019; Stefaniak, Alyahya, & Lambon Ralph, 2021). In line with this idea, Forkel and colleagues (2014) showed that the volume of the right AF was a predictor of the degree of severity of language impairment 6 months after a left hemispheric stroke. As regards to the functional laterality of the UF, the study from Emch and colleagues (2019) reported a bilateral frontal activation related to verbal WM, which might indicate the involvement of the right UF in healthy individuals. As for its structural lateralization, the previous literature shows inconclusive results regarding the hemispheric differences of the UF (Von Der Heide et al., 2013), although some reports point to a right-sided lateralization of the UF when comparing tract volume across hemispheres (Highley, 2002). The fact that the UF is not a strongly left-lateralized structure, or that it may even be right lateralized (as opposed to other language-related tracts, such as the long segment of the AF) might somehow facilitate the recruitment of its right hemisphere homologue after a left hemisphere lesion. Nevertheless, although greater right UF volume in healthy subjects might indicate stronger right fronto-temporal connectivity, it does not shed light on whether verbal STM is indeed supported by this structure. Therefore, it is not possible to directly infer its premorbid involvement in verbal STM functions in people with

chronic aphasia. While more research is needed to elucidate the role of the right UF in verbal STM in healthy speakers, an asymmetry favoring the right hemisphere suggests that the right UF, as a tract with relatively large volume, could be capable of supporting and assuming cognitive functions such as verbal STM as a result of brain plasticity, especially for PWA with large stroke-induced lesions on the left hemisphere.

Another possible interpretation would be that PWA, due to the language processing limitations caused by their brain injuries, may adopt compensatory strategies to complete the verbal STM tasks. In other words, they could rely on relatively more spared phonological mechanisms to perform lexical-semantic verbal STM tasks or vice versa. In fact, it has been previously described that the phonological representation of a word can help reactivate its semantic representation if it is not preserved at the time of evaluation, whereas purely phonological elements might be better remembered if they bear semantic implications (Jones & Macken, 2015; Martin et al., 2021). It is important to note that the potential interpretations presented above are not mutually exclusive. Actually, the right UF might support verbal STM in both healthy individuals and in people with post-stroke aphasia, only that in the latter group, this specific support function may especially emerge or increase after brain insult, maximizing the chances to regain verbal STM functionality.

We acknowledge some limitations in the current research, including the restricted sample size which may have reduced the statistical power to identify further relevant associations between white matter tracts and phonological and lexical-semantic STM. This may have influenced the number of significant correlations that finally survived the FDR corrections. In addition, the Language Competence Index was not independent from the verbal STM scores. Likewise, higher lesion volume increases the likelihood that a given tract is damaged. Thus, the partial correlations used may have somewhat underestimated the associations between structural and behavioral variables of interest. Another important limitation is the lack of a control group, which would have helped to clarify the possibility of premorbid involvement of the right UF in verbal STM, given the limited number of studies evaluating the white matter correlates of verbal STM in

healthy adult population. Furthermore, some aspects of the MRI data acquisition and pre-processing steps of the diffusion images could be improved. For instance, future studies could apply a denoising step or the new FSL eddy tool, which should improve to some extent the quality of the preprocessed images and therefore make it easier to detect differences between groups. Unfortunately, the specific imaging acquisition protocol used in this study precluded us from implementing these corrections. Finally, the massive lesions suffered by some of the participants in this study prevented us from reconstructing some of the tracts in the left hemisphere in a notable proportion of the sample. Although this hindered the identification of potential contributions of left hemisphere tracts to verbal STM, our main interest was to identify the white matter tracts that support verbal STM in people with chronic post-stroke aphasia and this constraint is inherent to their condition. Future work should complement our findings by studying white matter tract properties in larger samples of individuals with and without aphasia, in both the acute and chronic states of stroke, and with different lesion extents, in comparison to a healthy control group. This would help to establish if right hemisphere structures intrinsically support verbal STM or to understand if there are tipping points of lesion extent and time post onset that determine the engagement of right tracts over left hemisphere ones. In summary, future research could further corroborate to what extent the associations reported here are reflective of processes of plasticity and reorganization.

5. Conclusions

Our findings revealed a strong association between the volume of the right UF and measures of phonological and lexical-semantic STM, with the strongest association being with nonword repetition scores. This suggests that the right UF supports verbal STM in chronic aphasia. These results contribute to a better understanding of the white matter correlates of verbal STM after left hemisphere damage, and cerebral plasticity and compensatory mechanisms in chronic aphasia.

6. Statements and Declarations

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Disclosures
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Declaration of Competing Interest
None of the authors has competing interests to declare.

CRediT author statement
Guillem Olivé: Methodology, Investigation, Formal Analysis, Writing – Original Draft, Visualization **Claudia Peñaloza**: Conceptualization, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing **Lucía Vaquero**: Formal Analysis, Writing – Original Draft, Writing – Review & Editing **Matti Laine**: Conceptualization, Writing – Review & Editing **Nadine Martin**: Conceptualization, Resources, Writing – Review & Editing **Antoni Rodriguez-Fornells**: Conceptualization, Resources, Writing – Review & Editing, Funding Acquisition.

Availability of data and material
Anonymized data will be shared by request from any qualified investigator.

7. Supplementary material

Number of subjects with **missing tracts**	AF Anterior Segment	AF Long Segment	AF Posterior Segment	IFOF	ILF	UF
Left Hemisphere	13	12	8	8	1	8
Right Hemisphere	3	9	7	1	0	0

Supplementary Table 1 – Number of missing tracts Total number of participants for which each tract or segment could not be reconstructed in each hemisphere with the manual deterministic tractography. Abbreviations: AF = Arcuate Fasciculus, UF = Uncinate Fasciculus, ILF = Inferior Longitudinal Fasciculus, IFOF = Inferior Frontal Occipital Fasciculus.

Covariates	NW repetition x Volume of Right UF		Pointing Composite x Volume of Right UF		Repetition Composite x Volume of Right UF	
	Pearson r	p value	Pearson r	p value	Pearson r	p value
Probability of disconnection of the left UF	**0.749**	**>0.001**	**0.640**	**0.004**	**0.651**	**0.003**
Proportion of disconnection of the left UF	**0.669**	**0.002**	**0.501**	**0.034**	**0.574**	**0.019**
Probability of disconnection of the left anterior, long and posterior segments of the AF; left IFOF; left ILF and left UF	**0.838**	**>0.001**	**0.646**	**0.017**	**0.703**	**0.007**
Proportion of disconnection of the left anterior, long and posterior segments of the AF; left IFOF; left ILF and left UF	**0.578**	**0.039**	0.407	0.168	0.477	0.100

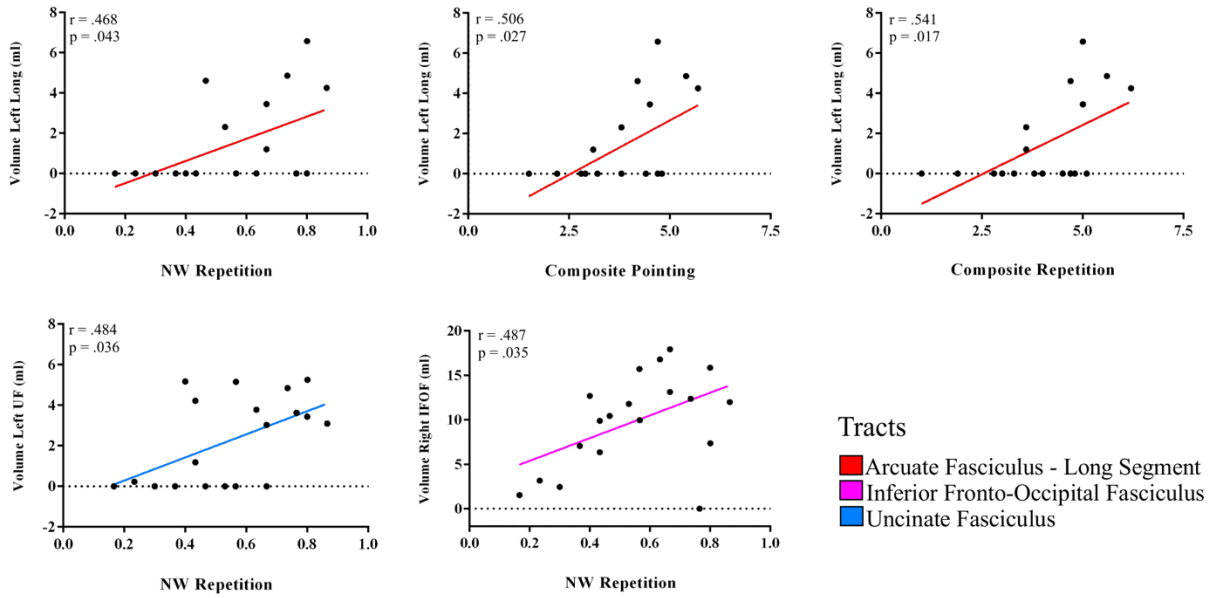
Supplementary Table 2 – Details of the partial correlations controlling for disconnection of left hemisphere tracts. Reanalysis of FDR-corrected significant results as partial correlations controlling for probability and proportion of disconnection of left hemisphere tracts. Bold numbers indicate uncorrected significant results at $p \leq 0.05$ level. Abbreviations: UF = Uncinate Fasciculus, AF = Arcuate Fasciculus, ILF = Inferior Longitudinal Fasciculus, IFOF = Inferior Frontal Occipital Fasciculus.

Tract	NW repetition		Pointing Composite		Repetition Composite	
	Pearson r	p value	Pearson r	p value	Pearson r	p value
Left AF Anterior Segment	0.145	0.554	0.179	0.464	0.125	0.611
Left AF Long Segment	**0.468**	**0.043**	**0.506**	**0.027**	**0.541**	**0.017**
Left AF Posterior Segment	0.378	0.110	0.248	0.307	0.252	0.297
Left IFOF	-0.006	0.982	-0.068	0.781	-0.013	0.959
Left ILF	0.366	0.123	0.138	0.573	0.177	0.468
Left UF	**0.484**	**0.036**	0.277	0.250	0.262	0.278
Right AF Anterior Segment	0.357	0.134	0.164	0.503	0.219	0.368
Right AF Long Segment	-0.110	0.654	-0.068	0.783	-0.216	0.375
Right AF Posterior Segment	0.390	0.099	0.290	0.228	0.242	0.318
Right IFOF	**0.487**	**0.035**	0.304	0.206	0.273	0.258
Right ILF	0.436	0.062	0.271	0.262	0.383	0.106
Right UF	**0.680**	**0.001**	**0.523**	**0.022**	**0.560**	**0.013**

Supplementary Table 3– Details of the correlational analysis for all volume measures. Uncorrected results obtained for the Pearson correlations performed between the three vSTM measures (NW repetition, Pointing composite and Repetition composite) and volume measures for each tract and hemisphere. Bold numbers indicate uncorrected significant results at $p \leq 0.05$ level. Abbreviations: AF = Arcuate Fasciculus, UF = Uncinate Fasciculus, ILF = Inferior Longitudinal Fasciculus, IFOF = Inferior Frontal Occipital Fasciculus.

Tract	NW repetition		Pointing Composite		Repetition Composite	
	Pearson r	p value	Pearson r	p value	Pearson r	p value
Left AF Anterior Segment	0.054	0.890	0.102	0.794	-0.052	0.894
Left AF Long Segment	0.381	0.277	0.546	0.103	0.465	0.175
Left AF Posterior Segment	0.196	0.563	0.057	0.869	-0.039	0.910
Left IFOF	-0.133	0.681	0.138	0.668	0.084	0.796
Left ILF	-0.159	0.516	-0.308	0.199	-0.278	0.250
Left UF	-0.172	0.556	0.240	0.409	0.104	0.723
Right AF Anterior Segment	0.171	0.526	0.135	0.617	0.091	0.739
Right AF Long Segment	-0.483	0.157	-0.301	0.397	-0.302	0.396
Right AF Posterior Segment	-0.352	0.262	-0.109	0.737	-0.094	0.771
Right IFOF	0.124	0.624	0.353	0.150	0.419	0.083
Right ILF	-0.231	0.342	0.025	0.919	0.148	0.546
Right UF	0.077	0.754	0.355	0.135	0.371	0.118

Supplementary Table 4 – Details of the correlational analysis for all FA measures. Uncorrected results obtained for the Pearson correlations performed between the three vSTM measures (NW repetition, Pointing composite and Repetition composite) and FA measures for each tract and hemisphere. Bold numbers indicate uncorrected significant results at $p \leq 0.05$ level. Abbreviations: AF = Arcuate Fasciculus, UF = Uncinate Fasciculus, ILF = Inferior Longitudinal Fasciculus, IFOF = Inferior Frontal Occipital Fasciculus.



Supplementary Figure 1 - Uncorrected significant correlations. Significant FDR-uncorrected correlations at the .05 level between tracts volume and vSTM scores. Figure adapted from Olivé et al., 2023.

Chapter 4 – General Discussion

Chapter 4 - General discussion

Language is a defining feature of the human species. Its acquisition begins at a very young age and is universal among neurotypical individuals (Fenson et al., 1994). However, from a logical point of view, this LA process should be a very complex process given the multiple problems and uncertainties a new learner must face (Sloutsky, Yim, Yao, & Dennis, 2017). As a result, LA has attracted huge attention, with several accounts investigating its basic mechanisms (Saffran, Newport, et al., 1996; Smith, 2000; Smith & Yu, 2008), proposing integrative models (Davis & Gaskell, 2009; Rodriguez-Fornells et al., 2009; Ullman, 2004) and examining its neural underpinnings (Karuza et al., 2013; López-Barroso et al., 2013; Ripollés et al., 2017). This latter aspect has been addressed mainly by studying the brain regions implicated in LA, whereas the role of white matter tracts in this process has been largely understudied.

The present dissertation tried to face this literature gap by examining the structural basis of LA. To that end, in the studies conforming this thesis, I used both behavioral and neuroimaging data to address this issue by characterizing the main language-related white matter tracts in the brain and relating its structural properties with LA performance. The key findings indicate that the integrity of LA in PLI is associated with the structural properties of both dorsal tracts (Study 3) and especially ventral tracts (Studies 1, 3, and 4).

The four studies have assessed LA from different perspectives: from the pre-language acquisition stage (Study 1) to its re-acquisition in the presence of neurodegeneration (Study 3), while also studying abilities closely related to LA, such as vSTM (Study 4). Moreover, the studies examined four different populations of PLI, namely nvASD, HD, PPA, and PSA. This granted a richer framework by evaluating processes that might be affected in each language impairment depending on their specific area of lesion/degeneration. Critically, it has also allowed addressing a secondary objective: assessing the integrity of LA at a behavioral level in these different populations.

The results obtained show that the success in LA processes is related to the structural integrity of several white matter pathways, mainly involving the anterior and long segment of the left AF, the IFOF and the UF. The results also suggest that LA is possible in PLI, although they generally exhibit lower levels of success in this process when compared to neurotypical individuals. These findings importantly contribute to expanding the theoretical models of language impairment and recovery, while opening avenues for potential clinical implications.

This section provides a general discussion of these main findings, interpreting them in light of our current knowledge in the field of language processing and LA. I will also elaborate on the importance of this kind of studies and their potential theoretical and clinical significance. Finally, I will consider the limitations of the present dissertation and suggest possible avenues for future research.

4. 1 Structural basis of LA

4.1.1 White matter tract functions related to LA: new insights from this thesis

The main objective of this thesis was to identify the white matter tracts relevant for LA. This aim was intended to be achieved by the characterization of the main language-related white matter tracts and its association with different LA-related performance in PLI. This goal was achieved, as several tracts were associated with different aspects of LA, as I will discuss in this section (see Figure 6 for a graphical depiction of the main results).

One of the white matter tracts that has been consistently associated with LA throughout this thesis is the **IFOF**. As described in the introduction, the IFOF is an associative tract that connects parieto-occipital regions with frontal areas (Catani & Thiebaut de Schotten, 2008; Duffau, 2015). It is a ventral language tract, so it has previously been associated with semantic processing functions of language, mainly (Griffis et al., 2017). Although research on the neural underpinnings of LA is scarce, the microstructural properties of this tract have previously been linked with success rates in a CTXL task in healthy adults (Ripollés et al., 2014). Regarding the present thesis, the results from Study 1 revealed that the microstructural properties of the IFOF are a differentiating feature of nvASD individuals compared to neurotypical controls. NvASD is usually defined based on its severe expressive language deficits (Tager-Flusberg & Kasari, 2013), although other accounts also report poor comprehension from this population (Slušná et al., 2021), which would greatly contribute to the general language problems exhibited at this end of the autism spectrum. Our results here suggest a disruption of the ventral language pathway –and the IFOF, specifically– in nvASD, in line with behavioral findings of semantic deficits in this group (Cantiani et al., 2016; Slušná et al., 2021). But these findings also indicate that the integrity of the IFOF could be important for language acquisition in its early stages. If the IFOF was indeed a key tract for LA, a disruption of this structure in the first years of life would deter the typical development of language observed in children. There is also the possibility that the alteration of the integrity of the IFOF would disrupt the ventral language stream (instead of the whole LA system), and that this would in turn affect specifically the semantic learning process. However, it is hard to think that an alteration in a sub-process of LA at such an early age could impact in such a specific manner, without disrupting the entire LA process. An alteration in the integrity of LA could explain the linguistic deficits observed subsequently in nvASD, both at the expressive and receptive levels. The suggestion of the involvement of the IFOF in LA is reinforced by the results of Study 3. In that case, we also found an association between its microstructural properties and the success of LA in older individuals (an association combining both neurotypical subjects and people with PPA). In the context of the task used in Study 3, it is possible that this tract has more of a semantic function within the LA process, participating in the extraction of the meaning of

new words from the context provided in each duplet of sentences. Nonetheless, both studies are coherent in suggesting an involvement of the IFOF in the LA process.

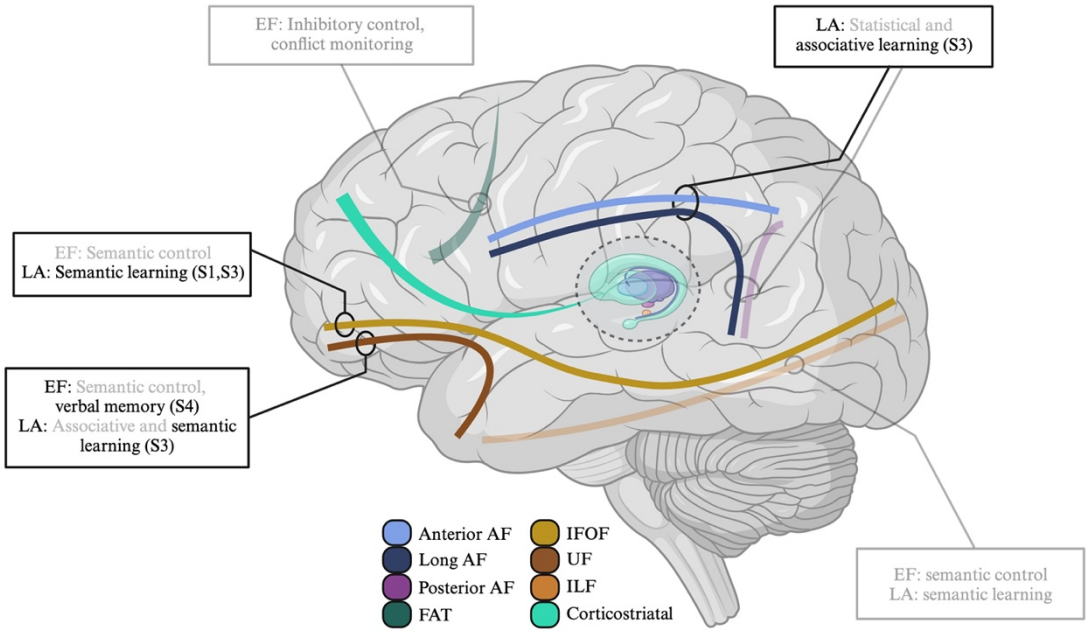


Figure 6. Potential language acquisition related functions of the white matter tracts investigated in this thesis. Summary of the white matter tracts related with language acquisition functions in this thesis and their possible functions according to the obtained results. The black text in the boxes displays the LA-related functions previously associated with each tract that could be supported by the findings in this thesis. On the contrary, light grey text shows the functions that were not tested or supported by experiments and findings in the present work. The numbers between brackets represent which study from this thesis could support each specific function proposed for each tract. Similarly, bright colors represent tracts for which we have evidence or suggestions of some LA related functions, while dull-colored tracts were not found to be related with LA functions according to this work. The dashed line aims to depict a window into subcortical structures of interest, which in this case would be the striatum. Abbreviations: EF = executive function, LA = language acquisition, S1 = study 1, S2 = study 3, S3 = study 3, S4, study 4, AF = arcuate fasciculus, FAT = frontal aslant tract, IFOF = inferior fronto-occipital fasciculus, UF = uncinate fasciculus, ILF = inferior longitudinal fasciculus. Figure generated with Biorender.com

Another tract that has been showed to be relevant for LA processes in this thesis is the **UF**. This tract connects temporal and frontal regions (Marco Catani & Thiebaut de Schotten, 2008). As a ventral language tract, it has been associated with semantic processing and semantic control functions (Harvey et al., 2013; Zhang et al., 2021), as well as memory (Christidi et al., 2014) and verbal learning (Ripollés et al., 2017, 2014; Rossi et al., 2017). The results from Study 3 show a relationship between the microstructure of the UF and verbal learning ability in the CTXL task. It is possible that this association has a similar origin as in the case of the IFOF, showing the possible involvement of the UF in LA for the meaning inference of the new words from contextual cues, specifically in our CTXL task.

There is another possibility, though: that the UF plays a role in LA processes by supporting vSTM functions. This is precisely what is suggested by the results of Study 4, which show a relationship between the volume of this tract and vSTM abilities in aphasic patients. This possibility would also align with findings from Study 3. Although in that Study we tried to minimize the vSTM load of the CTXL task in comparison with previous versions of the task, there is always a certain verbal memory component involved in any LA process that cannot be ruled out. As mentioned in the discussion of the Study 3, our CTXL task requires both the extraction of the meaning and the processing of the new word to be learned. The encoding and posterior association of both elements must be achieved to obtain a successful learning of each new word. It is possible that these two processes are carried out by different pathways (maybe belonging to different streams, too). This would imply that the information must be kept active and stored –at least for a short period of time– until the actual learning process has been completed, thus making vSTM skills also essential for successful LA. It is important to note that the UF could be involved in LA due to one of the two reasons discussed above, or both at the same time. Given that tracts have multiple origins and terminations, they connect different brain areas that could, in turn, be engaged in the different operations and subprocesses conforming LA.

The third tract that has been associated with LA in this thesis is the **AF**. According to the characterization applied here, this pathway is composed by three segments –anterior, long and posterior– which connect frontal, parietal and temporal regions (Catani et al., 2005). Unlike the previously discussed bundles, the AF is considered a dorsal language-route pathway and has been frequently linked to phonological processing and language production processes (Ivanova et al., 2021; Tremblay et al., 2019). In addition, it is possibly one of the tracts that has been most frequently related to the LA process, both in healthy population (López-Barroso et al., 2013; Ripollés et al., 2017; Su, Thiebaut de Schotten, et al., 2018) and in PLI, such as PSA patients (Coran et al., 2020; Tuomiranta et al., 2014). For this reason, it is not surprising that Study 3 has revealed an association between the microstructural characteristics of the anterior and long segments of the AF and the learning measures obtained from the CTXL task. The task design in said study does not allow us to tell apart the specific sub-process of LA supported by the AF. However, the studies cited above on the AF functions related to LA indicate the involvement of this tract in the acquisition of new phonological forms, possibly by means of statistical and/or associative learning mechanisms. Therefore, in the context of Study 3, the AF could also be supporting the learning of new word forms, possibly by an associative mechanism. In any case, this result goes in the direction of previous reports and is further evidence of the involvement of the AF in LA processes.

Finally, it is important to comment on the possible role of the striatum and its cortical connections within the LA process. The main result of Study 2 shows how LA is impaired in individuals with HD compared to neurotypical individuals. The design of this experiment was not aiming to depict a comprehensive picture of the underlying cerebral cause of said linguistic alterations. However, it is known that HD is characterized by the neurodegeneration of the basal ganglia, which is especially severe in the striatum. This also causes the degeneration of the regions that are connected with this structure, such as the frontal cortex, as well as the deterioration of the connections themselves (Haber, 2016). Consequently, it could be hypothesized that the LA impairments observed in this population might be, to some extent, secondary to its characteristic striatal degeneration. In fact, it has been argued that the striatum plays a central role in language processing at different levels (phonetics, phonology, morphology, syntax, and lexico-semantics) by regulating and controlling the allocation of limited cognitive resources to the different activities involved in linguistic functions (Jacquemot & Bachoud-Lévi, 2021b). Considering this possible central role of the striatum in language processing, it would be reasonable to think that this structure might also be involved in LA processes. More specifically, it could be related to the semantic integration process, which can be defined as the capacity to integrate the meanings of words across different contexts in order to properly capture the overall meaning of an utterance and to select the adequate lexical candidate in case of ambiguity (Rodriguez-Fornells et al., 2009; Van Berkum et al., 1999). A deficit in semantic integration would explain the impairments observed by HD individuals in the CTXL task in Study 2 and would align with the linguistic functions proposed for this structure. Obviously, all the proposed LA-related functions for the striatum would also apply to its connections, with a probable preponderant role of the frontostriatal ones. Since the aim of the thesis was to identify the white matter tracts relevant for LA, we must at least consider the possible involvement of the frontostriatal pathways in this process. However, more investigation would be necessary to confirm this possibility.

Overall, the results from this thesis have allowed the identification of a series of tracts that could be involved in the LA process to a greater extent than what was considered to date; namely the AF, the IFOF, and the UF (with a possible contribution of the corticostriatal pathways). These tracts might have different specific roles and support diverse sub-functions within the complex process of LA. More research will be needed in this direction in future studies to confirm or refute the results obtained here.

4.1.2 Fit of the results into the Integrative Neurophysiological Model (INM)

Apart from the identification of specific tracts, the results presented in this thesis are a broader demonstration that LA, just as it happens with language processing, relies on an extensive cerebral

network that engages multiple streams. Taking that into account, it is interesting to see how the present findings regarding white matter tracts engaged in LA fit with the already existing LA models. In this sense, the results obtained appear to align with the Integrative Neurophysiological Model (INM) of LA. According to this model, three main interfaces are engaged during the acquisition of language: i) a dorsal auditory-motor interface, important for the acquisition of new vocabulary; ii) a ventral meaning integration interface, more related to word-to-meaning mapping; and iii) an episodic-lexical interface, which might play a role in the initial memory binding of a novel word form to a conceptual representation. The observations made in the different studies conforming this thesis support the proposal of this model, both in the division of functions for each stream and in their neural underpinnings.

According to the results of Study 3, the dorsal stream would be represented mainly by the AF, which connects several brain regions including the pSTG, SMG, vPMC and IFG. All these areas are included in the dorsal stream as originally proposed by the INM model (see Figure 4). Moreover, this stream would carry out the functions hypothesized for it by the model as this bundle could have been engaged in the acquisition of new verbal forms in the CTXL task applied in Studies 2 and 3.

Similarly, the results from Studies 1 and 3 show the involvement in LA of two ventral tracts, the UF and the IFOF. These tracts connect regions possibly involved in the storage of conceptual/semantic information (the ITG and MTG in the case of the IFOF, and the ATL for the UF) with the IFG, which is potentially involved in the control of semantic retrieval. Moreover, the IFOF also presents terminations in the MFG, an area related to inductive reasoning. Therefore, given the functions of the regions connected by these tracts, their integrity would appear to be fundamental for the LA process, and specially for a CTXL type of learning. Furthermore, this notion matches the proposal of the INM model stating that the ventral stream (in this case represented by the UF and the IFOF) could support the word-to-meaning mapping in LA. This is supported by the associations presented in Study 3 (between CTXL performance and the integrity of the left IFOF and bilateral UF), and by the alteration of the IFOF observed in nvASD individuals in Study 1, which could be related to the linguistic deficits observed in nvASD.

Another set of results (Study 4) point to the involvement of the UF in vSTM functions, and a similar relationship between the UF and LA cannot be ruled out in Study 3. Numerous accounts have associated LA with vSTM capacity, both in healthy participants and in PLI (Freedman & Martin, 2001; Gathercole, 2006; Peñaloza et al., 2015, 2017). In addition, recent studies have pointed to the IPL and IFG as possible important sites for vSTM functions (Randi C Martin et al., 2021). Given that the IFG is one of the terminations of the UF, this thesis' results would support

these recent claims, suggesting the involvement of the IFG and the UF in an ability closely related to LA such as vSTM. In addition, this conclusion would complement the INM model, which do not incorporate these notions and may require an update in this regard.

Finally, the INM model attributes functions related to the control and modulation of information to the basal ganglia, including the selection of the appropriate lexical items in case of uncertainty or during integration of meaning. Although this cannot be confirmed by the present thesis, the results from Study 2 seem to align with this proposed role of the striatum and the cortico-striatal connections.

In short, the structural bases of LA as revealed in this thesis largely coincide with the ones proposed by the INM model. Although some aspects of the model were not evaluated –such as the cerebral bases of the episodic-lexical interface, since the main object of study were the associative language-related white matter tracts– the aspects of the model that were evaluated in the thesis support the validity of this model.

4.2 Considerations for the investigation of the structural bases of LA

In the introduction of this thesis, I discussed the paradigm shift experienced in the field in recent years, moving towards a more connectivist approach in the study of human cognition. We thus now understand that cognitive functions mainly rely on networks formed by multiple brain regions and connections. The results of this thesis are another piece of evidence in support of this view. The studies presented here associate LA with different structural measures of different tracts that belong to both dorsal and ventral language streams, and from both brain hemispheres. Therefore, one of the first conclusions that we can draw from the studies presented here is the need to carry out comprehensive studies that incorporate all these different elements when investigating language processing or LA, avoiding the temptation of focusing on a single white matter tract, a single hemisphere or a single structural measure. If we see language as a connectome, understanding language impairments as disconnectomes might be a good way of staying on track and following this network approach (Dronkers et al., 2017). Therefore, in the following section I will discuss some of these important aspects that should be considered when trying to uncover the white matter tracts involved in any language process -such as LA- or any cognitive process whatsoever.

4.2.1 LA: selection of white matter tracts and relevance of ventral tracts

An example of an important element to consider when studying the basis of LA is the white matter tracts to be investigated. Unlike previous studies focusing on a specific tract, I decided to include the main language-related white matter tracts in the three studies of this thesis in which neuroimaging was used. This decision was motivated by the idea of contributing to our understanding of the language connectome, which I consider a key concept of the dissertation. In this sense, the present results highlight the importance of evaluating different tracts belonging to the two streams. Indeed, different aspects of LA were associated here with various tracts, namely the IFOF –in Studies 1 and 3–, the left long and anterior segments of the AF –in Study 3–, and the UF bilaterally –in Studies 3 and 4–.

By evaluating the main language white matter tracts in different studies, some results can be analyzed transversally to uncover common patterns between them. One such case is the fact that ventral tracts have been observed to be linked to LA in Studies 1, 3 and 4, while only one of the studies (study 3) showed a relationship between LA and the dorsal tracts. These findings raise an important question: could the integrity of the ventral stream have a more preponderant role in the LA process than the dorsal stream? A large number of studies have shown that the two language streams present a division of tasks at a functional level, both in language processing and in language learning (Hickok & Poeppel, 2007; Lopez-Barroso et al., 2011). As previously mentioned, the dorsal stream is related to the acquisition of novel word forms (López-Barroso et al., 2013) whereas the ventral stream is associated with semantic learning (Ripollés et al., 2017). Although there is some anatomical overlap between streams in the areas they connect that could enable a compensatory effect of their function in case of impairment, previous studies show that this kind of compensatory processes produce sub-optimal results (Lopez-Barroso et al., 2011). Therefore, the ability to perform LA-related subprocesses largely depends on the integrity of the stream they mostly rely on (for instance, the semantic learning subprocess might rely mostly on the ventral stream).

It is clear that optimal LA depends on the integrity of the entire language network. However, in light of the results obtained here, it is tempting to ask the question of whether there might be one of the streams with greater importance for LA than the other. The disruption of the dorsal stream, in principle, would prevent the learning of new word forms, while disruption of the ventral system would prevent the acquisition of new verbal meanings. Thus, this transforms the initial question into whether it is more important to acquire word forms or word meanings, or in other words, what are linguistic labels worth without meaning. Even if a learner was able to acquire new verbal forms, they would become empty labels without any practical use if no meaning or real-world object representation could be assigned to them. Conversely, the acquisition of meaning could

still be relevant to an individual even if not all concepts could be assigned to a word form. This difference in relevance between streams in LA processes could partly explain the results obtained in Study 1, where an alteration of the ventral stream was associated with such dramatic results as the lack of language development in nvASD infants. It is important to highlight that the results obtained here do not show in any case that there is any order of importance between the different verbal streams in relationship to LA. However, the different associations obtained for each stream in relationship to LA makes this an interesting topic to ponder over, and one that could be explored in future research.

4.2.2 The role of the right hemisphere

Continuing with the idea of the need to study the language network from a global and comprehensive point of view, another factor that requires attention is the involvement of the right hemisphere in LA. In two of the studies of this thesis (Studies 3 and 4), significant correlations were reported between LA measures and structural properties of white matter tracts of the right hemisphere. A first interpretation of these results would be that, in the event of alterations in the left hemisphere, the right hemisphere could become engaged in the process of LA, for instance by plasticity and compensation mechanisms. In this case, we would be assuming that the LA depends mainly on the left hemisphere. This interpretation would be in line with reports and classic models describing language as a function primarily lateralized to the left hemisphere (Gazzaniga, Ivry, & Mangun, 2009). To reach this conclusion, studies on language processing have focused, among other things, on the difference between hemispheres in terms of volume and activation of the language-related cortical regions, or the volume or microstructural properties of the language tracts (Forkel et al., 2014; Okada et al., 2010; Vaquero et al., 2017). Based on this, it has been possible to observe how some structures like the long segment of the AF tend to be lateralized to the left hemisphere* (Catani et al., 2005; Thiebaut de Schotten et al., 2011). Consequently, the dorsal language stream has also been considered as left-lateralized (Hickok & Poeppel, 2007). Conversely, ventral tracts such as the ILF or the IFOF are anatomically more bilaterally distributed or similarly balanced between both hemispheres (Forkel et al., 2014), and functionally, the ventral stream is also considered to be recruited bilaterally (Hickok & Poeppel, 2007). Therefore, we see there are differences in the described lateralization patterns depending on the language stream studied. This distinction is relevant for the results obtained in this thesis: two studies (Studies 3 and 4) showed LA significantly related to right hemisphere structural connections and, in both cases, they were tracts belonging to the ventral stream. The fact that the ventral tracts are bilateral at a structural level could have important implications in these cases

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*It is important to emphasize that the studies that investigate the lateralization of white matter tracts are carried out, in their majority, in right-handed neurotypical individuals. These lateralization results may vary when studying left-handed individuals (Johnstone et al., 2021). In the same way, it has been reported that the tracts' lateralization degree can vary depending on sex and age (Catani et al., 2007). Therefore, these limitations must be taken into account when generalizing or drawing conclusions about bundles' lateralization.

given that a left hemisphere lesion affecting these tracts could be more easily compensated by engaging their right hemisphere homologs (Sierpowska, 2017). This possibility appears to be supported by our findings here. In Studies 3 and 4, a left hemisphere lesion did impair LA and its related processes but did not fully disrupt it in the patient cohorts.

However, this hypothesized compensatory effect of the right ventral tracts does not match with the results obtained in Study 1. As a matter of fact, this study presents a series of peculiarities that differentiate it from the rest: (i) it is a study on children, and (ii) it does not target language re-acquisition or acquisition of new words to be added to a pre-existing linguistic repertoire, but rather the acquisition of the first language (L1). In this case, in which the bases of linguistic knowledge are beginning to form, it is expected that all linguistic structures –dorsal and ventral, bilaterally– would be involved and would be necessary for this process to unfold normally (with a potential preponderant role for the ventral structures, as discussed in the last sub-section). Therefore, a disruption of this network at this stage of development might have had an irreparable impact on the studied population, preventing the acquisition of language in the first place. In this first interpretation of the results, I have assumed that the relationships found in our studies between LA and right hemisphere tracts are a consequence of adaptative mechanisms after brain insults. Nonetheless, there is another possibility: the right hemisphere might already be engaged in these functions at baseline, in the neurotypical population. Indeed, the correlations reported in Study 3 include both PPA and neurotypical controls, indicating that the relationship found between the right UF and the CTXL measure involves all these different individuals. In Study 4 we cannot know whether the relationship between UF and vSTM would also exist in the neurotypical population or if it is exclusive to PSA individuals at a chronic stage as there was no control group in this case. In line with these ideas, though, a large body of research has revealed that successful linguistic communication in the healthy brain relies on both hemispheres and not just the left one (Dronkers et al., 2017). Imaging and behavioral research on both healthy and clinical populations have revealed that the right hemisphere participates in the recognition of concrete words, plays a fundamental role in the processing of pragmatic and paralinguistic aspects of language, and has also been linked with orthographic processing (Dronkers et al., 2017; Lindell, 2006). Therefore, it is plausible that the relationships reported in the present studies simply show the basic engagement of these tracts in the LA process.

Notwithstanding, the results obtained here, jointly with a growing number of other studies, suggest that the right hemisphere is engaged in multiple aspects of language processing in neurotypical individuals (Federmeier, Wlotko, & Meyer, 2008; Lindell, 2006; R. L. C. Mitchell & Crow, 2005), which points to the need of investigating right hemispheric structures in all future studies in this field. Not doing so would mean neglecting a potential important part of the LA network.

4.2.3 The importance of the structural measures chosen

Another element to take into account for future studies investigating the bases of LA is the measures chosen for the characterization of the structural properties of white matter tracts.
Different measures can be obtained from the white matter tracts to characterize both their macrostructure and microstructure properties. In the studies included in this thesis, the chosen ones were the tracts' volume (Studies 1 and 4), FA (Studies 1 and 4), and RD (Studies 1 and 3). The measures chosen can greatly determine the obtention of a result as well as its interpretations. An example of this is found in Study 1, in which significant results were obtained for the 3 measures studied (volume, FA, and RD), but only the FA measure showed significant differences between the nvASD group and the control group. Similarly, in Study 4 both volume and FA were extracted, but only the former showed significant correlations with the behavioral vSTM measures.

The reason for these differences lies in the fact that each measure reflects different properties of the tracts, and their variation can be attributed to distinct underlying biological processes (Aung et al., 2013). Regarding the measures used in the experiments of this dissertation: i) Volume is thought to reflect intrinsic characteristics of the tracts like fiber-packing or tract-surrounding vasculature and glial architecture (Vaquero et al., 2021); ii) FA can be modulated by factors such as axon diameter, fiber organization and coherence, or membrane permeability (Friedrich et al., 2020; Winston, 2012), and; iii) RD has been related to the number of axons, axon density, and especially to the myelination degree (Ripollés et al., 2017; Song et al., 2005; Zatorre et al., 2012). Therefore, depending on the nature of the underlying biological mechanisms that cause the processes studied, they may or may not be captured depending on the specific structural measure chosen for the study. The message that can be extracted from this is that researchers should try to extract the structural parameters based on the biological mechanisms that are hypothesized to be related to the cognitive process studied. That is if that information exists or if there's a hypothesis about it. Either way, DTI studies should also try to include several measures of different nature (macro and microstructural measures like volume and FA, summary and non-summary measures like FA and RD, etc.) in order to maximize the ability to capture relevant results. Obtaining results with one measure and not another can be a limitation in some cases but can also be seen as a tool that can provide clues about the cellular processes involved in a given observation. In my opinion, combining measures is the way of obtaining a bigger, more complete picture of the processes studied, and that is why I opted for this approach in the studies contained in this thesis.

4.2.4 The characteristics of the LA task

Throughout these lines, I have repeatedly emphasized the scarcity of works assessing the structural basis of LA processes, as well as the necessity to carry out these studies. Yet, the evaluation of this capacity is nothing but challenging due to the intrinsic complexity of LA itself. This complexity arises from the fact that any LA process requires the engagement of other cognitive processes and domains that are closely but not solely related to LA. These include, among others, language processing (both at the phonological and semantic level), executive functions (including attention or vSTM) or long-term memory (Peñaloza et al., 2022). All these processes, as well as their associated brain regions and intrinsic structural connectivity, can get involved to a greater or lesser extent depending on the specific characteristics of each LA task, such as the difficulty and duration of the task, the type of stimuli or their presentation modality. For example, the AF has been repeatedly associated with auditory processing (e.g., Vaquero et al., 2021), so LA tasks in which the stimuli is presented orally might engage this tract and its connected areas more (López-Barroso et al., 2013) than another LA task in which the stimuli is presented visually (Ripollés et al., 2017, 2014), in which case it might involve other structures associated with reading and visual processing such as the IFOF (Kumar & Padakannaya, 2019; Arrington et al., 2017), for instance.

All these aspects must be taken into account when carrying out a LA study, especially when investigating LA in PLI (e.g., Tuomiranta et al., 2014). Firstly, when designing and elaborating the stimuli to control –or at least to try to minimize– all these LA accessory functions. An example of this could be the adaptation of the CTXL task adopted in Study 3, in which the pairs of sentences in each trial were presented in their entirety on the screen (instead of the word-by-word original presentation approach) in order to reduce the vSTM load of the task. Secondly, for carrying out a proper analysis of the data, that evaluates the contribution of these cognitive processes related to LA (when such information is available). Thirdly, to be aware of the complexity of LA processes and accordingly adjust the interpretation of the results and the robustness of the conclusions withdrawn from it.

In summary, the contribution of various linguistic and extralinguistic domains must be taken into consideration when evaluating the mechanisms and bases of the LA process. However, the complexity of evaluating this process should not get in the way of designing and developing more studies such as the ones presented here. In my opinion, efforts to innovate in our research approaches to keep studying these functions is paramount to shed light on the mechanisms and bases of LA processes which, as mentioned earlier, is a crucial process for any individual throughout their entire lifespan.

4.3 Patient studies

4.3.1 Advantages of patient studies

In this thesis I have investigated the bases of LA by studying different PLI. As mentioned in the introduction, studies with patients offer a window of opportunity for the assessment of cognitive processes, while exploring different diseases for the investigation of the same cognitive process can result in the obtention of more complete information.
On the one hand, investigating different PLI in the present work allowed the study of different aspects and stages of LA. In Study 1, I investigated the initial stages of LA while in Study 3 I evaluated LA at a later life stage. In addition, I was also able to evaluate cognitive processes that are crucial for LA –but do not constitute LA per se– such as executive functions (Study 2) and vSTM (Study 4).

On the other hand, the idiosyncrasy of the different profiles of PLI studied here enabled the investigation of the involvement of different brain regions and connections in reference to LA. Study 3 uses as framework the well-understood patterns of brain degeneration previously described for PPA, usually affecting left frontal areas in the non-fluent variant and left temporo-parietal regions in lvPPA participants (Maria Luisa Gorno-Tempini et al., 2004). In Study 4, the pattern of affected regions was assumed to be more heterogeneous as it included a sample of PSA patients that presented a variety of affected cortical and subcortical lesions in the left hemisphere. In Study 2, despite not acquiring any neuroimaging data, the probable region of degeneration in the striatum and its connections is assumed since these are the structures typically affected in HD (Rüb et al., 2016). In these three cases, our team was able to explore the contributions of these structures to the LA process by assessing the impact of the damage in these regions to the patients' LA performance. In terms of the study of affected regions, the reasoning behind Study 1 was different from the other studies. In this case, we did not know which cortical areas were affected beforehand –if there was any–, only which linguistic impairments were presented by the population of study. Therefore, Study 1 allowed us to uncover the possible neural structures responsible for the observed linguistic features in nvASD.

At this point it is important to note that in most studies presented here (Studies 1, 3, and 4), the behavioral assessment of PLI was combined with the use of neuroimaging techniques. This is relevant since both approaches have their strengths and weaknesses, but they can both complement each other. Moreover, these two approaches provide evidence of different nature: a focal lesion in a brain region with an indispensable role for a certain process can reveal a causal relationship between that neural location and LA, while the results of imaging studies are

correlational by necessity (Chatterjee, 2005; Mirman, Chen, et al., 2015). Despite offering complementary information, the relative weight of these two approaches within academia has undergone a very different evolution in recent years. Specifically, a decrease in the number of publications and citations of lesion studies contrasts with an opposite trend for neuroimaging studies (Chatterjee, 2005). These different tendencies might be caused by multiple aspects, including the difficulty faced by researchers to find and access patients in injury-related studies, to maintain a given sample (due to frequent dropouts and health problems in patients), or the regulatory burdens of patient research. This contrasts with the appeal and novelty of imaging studies and its relatively easier access to data (Chatterjee, 2005).

This text does not intend to disparage any technique or to elevate any other, but rather to highlight the need to understand the advantages and disadvantages of each one, to try to choose the best one according to the research questions, and to combine them when possible. Despite the multiple technological advances, studies with patients continue to represent a necessary source of knowledge for rigorous research about the mechanisms and bases of cognitive processes (Vaidya, Pujara, Petrides, Murray, & Fellows, 2019).

4.3.2 Insights obtained from our patient studies

At a theoretical level, I previously mentioned how studies with PLI could help uncover relevant structures for LA. In that sense, the four studies presented here have revealed the contribution of different white matter tracts –namely the AF, the UF, and the IFOF– in the LA process (as well as a possible contribution of the corticostriatal pathways in executive functions supporting LA). These findings also suggest the involvement of the whole language system in LA functions, albeit different structures might support different specific subprocesses. These conclusions not only allow us to improve the existing theoretical models about LA (see Figure 6), but they also help to identify the altered structures that might be responsible for the language alterations observed in some specific language impairments.

Along these lines, I also previously argued that studies with PLI could inform about the preservation of LA-related mechanisms or processes in the presence of brain damage. The studies presented here have allowed to determine that CTXL is still possible in the different linguistic impairments assessed, although it appears to be generally weakened in comparison to neurotypical individuals. They have also revealed differences between patient profiles in terms of their affected mechanisms (semantic word learning impairment in PPA, or executive dysfunction with preserved semantic processing in HD), as well as differences in the LA integrity within patients presenting the same condition (nfvPPA appear to perform better than lvPPA in CTXL). These results expand our knowledge about which linguistic skills may be preserved or not in the

different linguistic disorders, depending also on the level of structural brain network integrity in each case.

Additionally, the knowledge obtained from this thesis could also have transferability to the clinical field. As mentioned in the introduction, assessing the integrity of LA can help improve the classification of patients into different subtypes or variants, which in turn may improve the therapeutical / rehabilitative approaches that medical teams would prescribe for them. As an example, the classification of PPA patients into specific subtypes is often complex, but it is especially difficult for the two variants assessed in Study 3 –nfvPPA and lvPPA– considering their common characteristics in early stages of the disease (Hinkley et al., 2023; Volkmer et al., 2020). One of the main results of this study shows that individuals classified as nfvPPA present significantly greater learning scores than lvPPA individuals in a CTXL task. Consequently, if the results obtained here were to be confirmed in future studies, the preservation of LA functions could be a feature that could help distinguish these two profiles of PPA patients.
Yet, the results obtained in this collection of studies may also be relevant for the management and treatment of PLI. LA has been proposed to have a central role in the recovery following language therapy (Coran et al., 2020b), but the results show that there might be major differences between diseases, or even between patients sharing the same diagnosis, in terms of preserved status of LA. However, LA can be achieved in several ways or by exploiting different mechanisms, as explained in section *1.3.2.1* of the introduction. Therefore, the results presented in this dissertation should highlight the need to evaluate the integrity of the different LA mechanisms in different impairments. This evaluation should be done systematically, as it would allow rehabilitation strategies to be adapted to each patient, exploiting the mechanisms that are preserved and that can maximize the chances of recovery for each patient while also improving the affected skills.

In conclusion, results from the studies included in this thesis show the need and relevance of conducting patient studies, given the rich advances they can provide, despite the multiple methodological and logistical challenges that they may pose. I am convinced that this type of studies is essential for obtaining rigorous and reliable results in the field of cognitive neuroscience research, in the LA topic, in particular.

4.4 Limitations and future directions

This work presents some limitations that must be acknowledged.
The structural neuroimaging techniques used here present several inherent shortcomings. First, as explained in the introduction, deterministic tractography on DTI data assume a main diffusion direction per voxel. However, this fiber orientation classification might be deficient in cases of

crossing, kissing or fanning fibers (Figley et al., 2022), and this can affect the final reconstruction output. Moreover, manual dissection of white matter tracts entails potential experimenter bias related to the placement of the regions of interest determining the final output. Besides, the biological processes related to the changes of each macro and microstructural measures are still far from being fully understood (Beaulieu, 2002). All the above-mentioned pitfalls call for caution when interpreting the results from the different studies. Future studies could try to replicate the results obtained here and investigate the white matter tracts associated with LA by using alternative approaches, such as different acquisition strategies (e.g. HARDI), models (e.g. CSD), or tractography algorithms (e.g. probabilistic). These options should partially reduce the methodological weaknesses of the studies and confirm (or not) the obtained results.

Another limitation present in this work, especially in Studies 3 and 4, is the limited sample size, which may have hindered the statistical power of the study and prevented the identification of some significant associations between LA measures and white matter tracts' characteristics. As discussed in a previous section, patient studies entail a series of difficulties related to the recruitment of participants and the maintenance of the sample throughout the experiment. Therefore, this limitation must be acknowledged even if it is difficult to remediate, in most cases.

Furthermore, the results of this thesis represent a first step towards understanding the cognitive mechanisms involved in LA and its neural bases. However, it is possible that other factors apart from the characteristics of the white matter tracts conditioned the differences observed between groups in the studies presented here. We have already seen that LA is a very complex process, related to multiple extra-linguistic cognitive processes such as attention (MacRoy-Higgins & Montemarano, 2015), vSTM (Bormann, Seyboth, Machleb, & Weiller, 2020), or motivation (Ripollés et al., 2016), among others. Therefore, future research should try to discern what is the contribution of factors outside linguistic abilities (especially with regards to executive functions) in LA performance in different PLI like the ones observed here. Also, particular characteristics and/or damage to specific cortical and subcortical structures may also contribute to the findings displayed here, in combination with the white-matter connectivity markers studied here.

The limitations discussed above affect all the work presented in this thesis. Nevertheless, some aspects regarding the design of each individual study could have also been improved or further explored. I will present these points for each individual study, although most of them have already been discussed or mentioned in each study's specific discussion section.

Study 1 revealed a significant group difference in the microstructural characteristics of the IFOF between nvASD and neurotypical controls. However, we cannot rule out the possibility that the

observed differences were due to a maturation delay of the white matter pathways in the affected group and that, over time, these differences could disappear or be reduced. To verify this possibility, future studies should opt for a longitudinal approach to observe the pattern of microstructural changes of these white matter tracts over time in nvASD individuals.

Results from Study 2 suggested a possible role of the frontostriatal tracts in the LA process. However, the absence of neuroimaging techniques calls for caution when drawing this conclusion. This limitation could have been addressed by obtaining DWI data from participants and dissecting the frontostriatal tracts in order to correlate its characteristics with the CTXL task measures. Although we did not have the opportunity to obtain this data, future studies could explore this, potentially helping to get a clearer picture about the involvement of the striatum and corticostriatal tracts in LA. Moreover, if this line of research is ever pursued, it would allow for a more direct exploration of the effect of motivational aspects in LA. Previous research has shown that reward and motivation can facilitate word learning (Ripollés et al., 2016), and that new word-learning activates the striatum (Ripollés et al., 2014). Therefore, the striatum appears to have an important role in LA not only by semantic integration processes, as suggested by the results of Study 2, but also by the inherent motivational aspect of language learning. Thus, tasks could be modified / designed to evaluate the effect of motivation in learning in HD individuals, for instance by testing the difference in learning outcomes when learning non-relevant versus personally relevant items, relating then these differences to the characteristics of the corticostriatal tracts.

In Study 3, the inclusion of a group of semantic variant PPA individuals could have helped to corroborate the involvement of tracts reaching anterior temporal regions (such as the UF, and possibly the ILF) in the LA process. It might have also showed potential LA differences between that group and the ones already tested in this study (namely, nfvPPA and lvPPA), which could have further confirmed the possibility to classify PPA individuals into different variants based on their LA integrity.

Finally, Study 4 revealed an association between the properties of the UF and vSTM preservation. However, the lack of a control group here prevented us from discerning if the obtained results show a premorbid involvement of the right UF in verbal STM or if, on the contrary, they are a consequence of adaptive mechanisms following stroke in PSA individuals. Future studies should resume and expand this venue of research by including a neurotypical control group in order to clarify this matter.

Despite the limitations of the studies within this thesis, the results successfully achieved the primary goal of uncovering the white matter tracts involved in language acquisition processes in the presence of language impairment. Thus, the findings presented here offer significant contributions to both theoretical understanding and clinical application in the field of language acquisition and provide a valuable foundation for future research.

Chapter 5 – Conclusions

Chapter 5 - Conclusions

In this dissertation I aimed to investigate the white matter structural bases of language acquisition (LA). For that purpose, I used a combination of diffusion MRI data and behavioral measurements of different aspects of LA. Crucially, the four studies conforming this thesis were focused on groups of People with Language Impairment (PLI). This approach was planned not only aiming to improve theoretical models of language impairment and recovery, but also taking into account potential clinical implications. Additionally, it allowed me to address a secondary objective: assessing the integrity of LA at a behavioral level in these different populations.

The main finding of the thesis indicates that the integrity of LA in PLI is associated with the structural properties of several white matter language tracts belonging to both the dorsal and the ventral streams. The specific pathways that were associated with LA were the anterior and long segment of the AF, the IFOF, and the UF, and present findings suggest a possible specific engagement in different sub-processes of LA. I proposed that the former two tracts might be related to phonological aspects of LA, while the latter two could be more related to semantic learning, although this division of functions would require further investigation. The results from Study 4 showed that the UF is also related to vSTM functions in PSA individuals. Moreover, the results from Study 2 suggest an involvement of the corticostriatal tracts (possibly the frontostriatal) in semantic integration functions.
Apart from the identification of specific tracts and their possible functions, the results from this dissertation confirm the complex nature of the LA process, which relies on an extensive cerebral network. In addition, the results obtained appear to fit well in the Integrative Neurophysiological Model (INM) of LA (Rodriguez-Fornells et al., 2009). According to the obtained results, the dorsal auditory-motor interface, proposed to be related to the acquisition of new vocabulary, would be associated with the integrity of the AF. On the other hand, the ventral meaning-integration interface, more related to word-to-meaning mapping, would be represented here by the IFOF and the UF. The current thesis also supports the proposed integrative role of the striatum in LA, and further complements the INM model by positing the UF and its cortical terminations with a central role in vSTM functions.

Regarding the secondary objective of assessing the integrity of LA in different PLI groups, the results obtained suggest that LA is possible in clinical populations, although they generally exhibit lower levels of success when compared to neurotypical individuals. Results also revealed that differences can exist within language impairments, as it is the case in PPA individuals. In Study 3, nfvPPA patients showed higher scores in the CTXL task than lvPPA ones, revealing potential

differences in the preservation of this ability depending on the regions and tracts affected in each case.

Overall, I think the findings and conclusions of this work contribute to enlarging our current knowledge regarding the structural neural basis of such a complex and fascinating human ability such as LA, and could stimulate future investigations on this topic. I believe these kinds of patient studies are fundamental given that the central role that has been evidenced for white matter tracts in LA processes does not match our current level of understanding regarding which tracts are implicated and in which specific roles.

Besides the theoretical advances implied by this work, the knowledge obtained could also have transferability to the clinical field. As mentioned across the dissertation, assessing the integrity of LA could help improve the classification of patients into different subtypes or variants, which could also be relevant for the management and treatment of PLI, advancing towards the ultimate goal of maximizing the chances of recovery and tailoring therapeutical approaches to each patient.

In conclusion, the assessment of the structural bases of LA is a crucial issue that needs to be pursued in future research. I think it is difficult to fully understand how we process language without knowing how we acquire it, given that these two processes are in constant interaction with each other throughout our lifespan. Therefore, the study of the structural bases of LA is essentially an advance towards a better understanding of human language processing and, by extension, a step towards a better understanding of human cognition.

Chapter 6 – References

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