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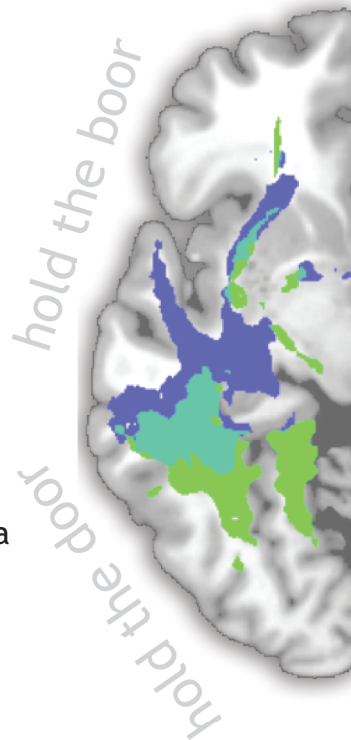
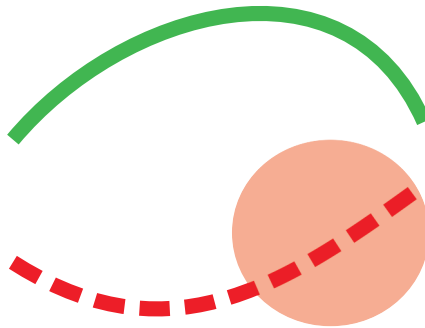
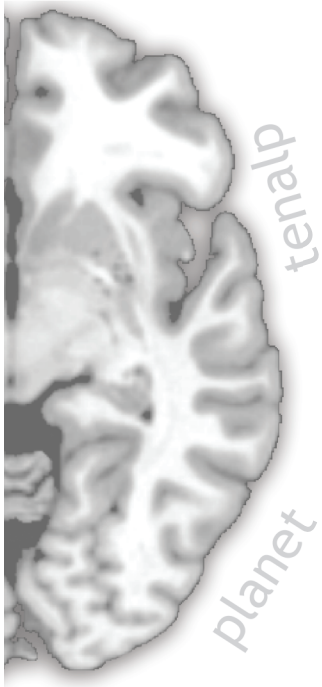


UNIVERSIDAD DE MÁLAGA

# **From dysfunctional to extraordinary verbal repetition abilities: clinical implications and neural features**

PhD Thesis

María Jose Torres Prioris




Departamento de Psicobiología y Metodología  
de las C.C. del Comportamiento

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# **From dysfunctional to extraordinary verbal repetition abilities: clinical implications and neural features**

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CERTIFICA:

Que Dña. María José Torres Prioris ha realizado bajo su dirección el trabajo “FROM DYSFUNCTIONAL TO EXTRAORDINARY VERBAL REPETITION ABILITIES: CLINICAL IMPLICATIONS AND NEURAL FEATURES”, que presenta para optar por el Grado de Doctor por la Universidad de Málaga.

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La idoneidad de la presentación de la tesis por compendio de publicaciones.

Así como que las publicaciones que avalan la tesis no han sido utilizadas en tesis anteriores.

Málaga, a 31 de octubre de 2019

Fdo. Marcelo L. Berthier

Fdo. Guadalupe Dávila Arias



*"The cosmos is within us. We are made of  
star-stuff. We are a way for the universe to  
know itself."*

*"Somos polvo de estrellas que piensa acerca  
de las estrellas. Somos la forma en la que  
universo se piensa a sí mismo".*

*— Carl Sagan*





*A mi familia*

*A ti, Diana*



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# Preface

Language is one of the most astonishing and complex cognitive functions of the human brain, which sustains our capacity for abstract thinking and communication. It allows us to create endless possible constructions, making feasible not just a basic communication, but to express (and think) in a completely novel and complex way.

Among language functions, the ability to repeat verbal information may seem one of the simplest. Yet, it requires the mapping between phonological and motor codes (i.e., auditory-motor integration), a process that involves many substages. Repeating a word in our native language is an easy task for most of us, but it may become more challenging if the sequence of phonemes to-be-repeated is meaningless (i.e., repeating a pseudoword) or too long; if it belongs to another language that contains different sounds, or if extra demands such as intermediate manipulations between input and output are imposed, for instance reversing the order of syllables (backward repetition, e.g., hear “basket”, and repeat “teksab”). Importantly, repetition, even of a single known syllable, may become a herculean task for persons with aphasia; and backward repetition, even of a full sentence (e.g., hear “I run because I am late” and say “etal ma I esuaceb nur l”), may be an easy task for a gifted person. Thus, repetition is subjected to variability, which can be explained by individual factors related to preservation of the neural language system, but also to anatomical and functional differences in the language networks.

Beyond the individual capacity for this function, verbal repetition invariably stands out as crucial for successful language learning throughout life and as a major resource in aphasia rehabilitation. Despite of this, repetition is an understudied function and for this reason the present doctoral dissertation aims to explore and get further knowledge on the cognitive and neural features of different states of repetition abilities (e.g., altered repetition, echolalic repetition) in people with different aphasia profiles as well as in healthy persons with an extraordinary language ability (i.e., backward speakers).





# Declaration

This dissertation contents original works including:

## 1. Published articles

**Torres-Prioris, M. J.**, López-Barroso, D., Roé-Vellvé, N., Paredes-Pacheco, J., Dávila, G., & Berthier, M. L. (2019). Repetitive verbal behaviors are not always harmful signs: Compensatory plasticity within the language network in aphasia. *Brain and Language*, 190, 16–30.

Berthier, M. L., **Torres-Prioris, M. J.**, & López-Barroso, D. (2017). Thinking on Treating Echolalia in Aphasia: Recommendations and Caveats for Future Research Directions. *Frontiers in Human Neuroscience*, 11, 164.

Berthier, M. L., **Torres-Prioris, M. J.**, López-Barroso, D., Thurnhofer-Hemsi, K., Paredes-Pacheco, J., Roé-Vellvé, N., ... Dávila, G. (2018). Are you a doctor? ... Are you a doctor? I'm not a doctor! A reappraisal of mitigated echolalia in aphasia with evaluation of neural correlates and treatment approaches. *Aphasiology*, 32(7), 784–813.

## 2. Onworking articles

**Torres-Prioris, M. J.**, Pertierra, L., López-Barroso, D., Dávila, G., Berthier, M. L. Are verbal repetition deficits over-represented in males? A systematic literature review on post-stroke aphasia

**Torres-Prioris, M.J.**, López-Barroso, D., Càmarà E., Berthier, M. L., García A. Language in reverse: Neurocognitive correlates of phonological encoding in backward speakers.

## Related publication that were not included in the present dissertation

Berthier, M. L., Dávila, G., & **Torres-Prioris, M. J.** (2017). Echophenomena in aphasia: Causal mechanisms and clues for intervention. In P. Coppens & J. Patterson (Eds.), *Aphasia Rehabilitation: Clinical Challenges* (pp. 143-172). Burlington, MA: Jones & Bartlett Learning.

Froudust-Walsh, S., López-Barroso, D., **Torres-Prioris, M. J.**, Croxson, P., & Berthier, M. L. (2018). Plasticity in the Working Memory System: Life Span Changes and Response to Injury. *The Neuroscientist*, 24(3), 261-276.

**Torres-Prioris, M. J.**, López-Barroso, D., Paredes-Pacheco, J., Roé-Vellvé, N., Dawid-Milner, M. S., & Berthier, M. L. (2019). Language as a Threat: Multimodal Evaluation and Interventions for Overwhelming Linguistic Anxiety in Severe Aphasia. *Frontiers in Psychology*, 10, 678.



# Abstract

Verbal repetition and audio-visual imitation stand as crucial functions for the acquisition and maturation of language in childhood, language learning in adulthood, and a major resource for language recovery after brain damage. Although modern neuroimaging techniques have allowed the identification of the brain areas involved in repetition tasks in healthy subjects, many clinical and neural aspects of this linguistic function are still overlooked in persons with aphasia and in emerging models of language expertise. Therefore, the present dissertation aims to explore cognitive correlates and neural features of verbal repetition from different perspectives including models of dysfunctional repetition (i.e., people with aphasia) and language expertise (i.e., healthy backward speakers). Generally, this thesis explores the potential of the dorsal and ventral components of the neural network supporting verbal repetition to assume, under certain circumstances (e.g., brain damage or extraordinary abilities), non-canonical functions. Further, this dissertation addresses clinical issues of some aphasic symptoms characterized by uncontrolled repetition (i.e., echolalia), as well as reviews sex as a source of variability in verbal repetition outcomes after brain damage.

**Chapter 1** expands the space-constrained background presented in the introductory section of each article included in this thesis.

**Chapter 2** presents the research aims targeted in each of the included studies.

**Chapter 3** presents the 5 studies that are part of this dissertation. First, it reviews the mechanisms involved in dysfunctional repetition, especially in two repetitive verbal behaviors named *conduite d'approche* and *mitigated echolalia* (Study 1) and addresses clinical issues of the last one (Study 2 and 3). In this regard, **Study 1** proposes that in the context of aphasia these symptoms (i.e., *conduite d'approche* and *mitigated echolalia*) may represent active attempts of verbal communication, rather than inconsequential repetitive verbal behaviors resulting from maladaptive neural changes. Three cases are presented to index the hypothesis that *mitigated echolalia* emerges from overreliance on the dorsal language stream, through the arcuate fasciculus, when the ventral stream is damaged; whereas *conduite d'approche* ensues when the ventral stream attempts to compensate a dorsal damage. The role of the right hemisphere and other alternative pathways in both cerebral hemispheres in the successful compensation of brain injury is also discussed. Further, **Study 2** reconceptualizes different types of *echolalia* within a continuous of severity and communication capacity. To accomplish this new instantiation, it is proposed that different types of *echolalia* may be associated to failure in distinctive linguistic and non-linguistic cognitive functions. Recommendations for its evaluation and treatment are provided,

suggesting that echolalia interfering with functional communication should be treated. Further, complementing the previous one, **Study 3** reports a comprehensive single case study exploring response to treatment, and behavioral and neuroimaging features of a person with mitigated echolalia associated to a chronic fluent aphasia. Findings from such case include a reduction of mitigated echolalia after two weeks of intensive aphasia therapy as well as the maintenance of these gains with memantine alone for at least 6 months. Importantly, reduction of mitigated echolalia instances in response to treatment speeded up the time needed to complete comprehension tasks. Neuroimaging results, although indirectly, suggested that mitigated echolalia may be supported by the activity of the remaining components of the left dorsal stream and compensatory right hemisphere recruitment.

Additionally, to further explore the neural and cognitive mechanisms involved in verbal repetition in a model of language expertise, **Study 4** tackles cognitive features and neural correlates of verbal expertise in two healthy adult subjects displaying an extraordinary ability to orally reverse language, a condition referred to as *backward speech*. Results suggest that phonological expertise, as shown in backward speech, involves reshaping (or pre-existent differences) of cortical areas and tracts relevant for auditory-motor integration and semantic processing. Greater functional coupling between critical language areas and domain-general and high-order visual areas may further support reversing processes. Lastly, **Study 5** presents a systematic review of the literature aimed to examine sex differences in the prevalence of repetition deficits in persons with post-stroke aphasia. Results show that the proportion of females in the group of aphasia characterized by repetition deficits (i.e., conduction aphasia) is lower than the expected by the prevalence of stroke among them. It is suggested that sex-related differences in the volume of areas of the right hemisphere homologues to the ones subserving repetition in the left hemisphere may be at the base of this difference. This finding poses sex as a relevant variable to account for variance in repetition abilities, and as a relevant factor to consider in future studies of language acquisition, maturation, and relearning promoted by aphasia therapy.

# Frequently used abbreviations

**PWA:** persons with aphasia

**CA:** conduction aphasia

**TCMA:** transcortical motor aphasia

**TCSA:** transcortical sensory aphasia

**MTCA:** mixed transcortical aphasia

**IFG:** inferior frontal gyrus

**IC:** insular cortex

**STG:** superior temporal gyrus

**MTG:** middle temporal gyrus

**ITG:** inferior temporal gyrus

**SMG:** supramarginal gyrus

**IPC:** inferior parietal cortex

**AG:** angular gyrus

**PMC:** premotor cortex

**SMA:** supplementary motor areas

**Spt:** Sylvian–parietal–temporal area

**VLSM:** voxel-lesion symptom mapping

**AF:** arcuate fasciculus

**SLF:** superior longitudinal fasciculus

**ILF:** inferior longitudinal fasciculus

**IFOF:** fronto-occipital fasciculus

**UF:** uncinate fasciculus

**FA:** fractional anisotropy

**STM:** Short-term memory

**WM:** Working memory

**BA:** Brodmann's area

**ECoG:** electrocorticography



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# CHAPTER 1



# Chapter 1. Introduction

## 1. Verbal repetition: an overview

The ability to repeat a just heard word (e.g., discovery) or phonological sequence (e.g., nedoniso) is an essential cornerstone of the language function, allowing the acquisition of language during childhood, learning new word forms during adulthood, and re-learn lost words after language impairment due to brain damage. Despite being a seemingly simple task, successful verbal repetition demands the succession of multiple subprocesses that rely on a dynamic interaction between sensory and motor areas that will ultimately enable the transcription of an auditory sequence into the articulatory code. In order to do so, a healthy speaker must first process the incoming sound (auditorily and phonologically), when possible link this sound to learned sequences stored in memory, maintain a precise representation in phonological short-term memory (STM) until interfacing that representation into the motor system to finally accurately articulate the sequence. (Hope et al., 2014; Majerus, 2013). Also, although not required, repeating a stimulus involves automatic imitation of some incidental aspect such as prosody, phonetic style or vocal pitch (Kappes, Baumgaertner, Peschke, & Ziegler, 2009). Yet, verbal repetition skills frequently change after brain damage in the left hemisphere, resulting in a decline in performance, the production of errors (e.g., paraphasias) or in the recurrent and excessive repetition of verbal material (echolalia). At the other end of the continuum, some gifted healthy individuals may develop extraordinary skills in some of the intermediate processes involved in verbal repetition which lead to outstanding language abilities as is the case of people with the ability to reverse language (i.e., backward speakers).

Cognitive, computational and neurocognitive instantiations of speech repetition converge in formulating two anatomical, i.e., dorsal vs ventral, and functional, i.e., lexical vs non-lexical, segregated streams supporting these processes. (Hickok & Poeppel, 2004; McCarthy & Warrington, 1984; Patterson, Shewell, Coltheart, Sartori, & Job, 1987; Ueno, Saito, Rogers, & Lambon Ralph, 2011) The dorsal stream appears intertwined to the mirror neuron system (Arbib, 2010; Corballis, 2010), playing both an important role in repetition/imitation functions. Yet, these systems are not immutable cable-like connections. Rather, an extensive corpus of evidence shows that behavioural training and cognitive strategies may reshape these networks leading, in some cases, to the improvement of language function after brain damage (Hartwigsen & Saur, 2017; McKinnon et al., 2017) and, in others, to outstanding linguistic abilities as it is observed in cases of language expertise (Elmer, Hänggi, & Jäncke, 2014; Elmer et al., 2019; Golestani, Price, & Scott, 2011; Vandermosten,

Price, & Golestani, 2016). Interestingly, pre-existing variability in the anatomical and functional architectures of these networks may also explain individual differences in language abilities (e.g., repetition) and recovery after brain damage (Catani et al., 2007; Forkel et al., 2014). With this on mind, in the *main corpus* of the present dissertation I will target overlooked neural, cognitive and clinical aspects of verbal repetition functions in people with aphasia (PWA) and in a model of language expertise. But first, this introductory chapter aims to broaden the background presented in each of the included articles, starting by stating the evolutionary, developmental and clinical importance of verbal repetition.

## **2. Relevance of verbal repetition**

The complexity of human language makes us unique and, this raise the question of what are the changes that shaped such an amazing capacity across evolution. Aboitiz (Aboitiz, 2018) proposed that one of the most relevant milestones in language evolution was the tuning of the neural circuitry sustaining auditory-motor integration systems, which is involved in auditory-verbal repetition and the articulatory rehearsal component of phonological STM/working memory (STM/WM). The development and maturation of this neural network is thought to have enabled our ancestors learning increasing complex phonological strings via repetition/imitation, allowing them to adapt to complex social environments (Aboitiz, 2018). It is to note that, speech is by nature an auditory-motor integration process shaped from feed-forward control by which perception modulates production and, at the same time, the motor system influence perception (Hickok, Houde, & Rong, 2011; Rauschecker & Scott, 2009).

As well, verbal repetition/imitation plays a key role in language acquisition, which involves learning new words. Phonological aspects of word-learning are essentially based in the capacity to perceive (and maintain) the phonological form of speech as well as in the ability to accurately reproduce the articulatory patterns combined on those sounds (Baddeley, Gathercole, & Papagno, 1998), all functions grounded into auditory-motor integration process. Wernicke was probably the first to suggest that this process plays a crucial role in language development (Wernicke, 1874). In fact, one of the most relevant point of Wernicke's model relies on the existence of an anatomical connection between the sensory (i.e., Wernicke's area) and motor (Broca's area) centers (Wernicke, 1874). In this line, a recent study has provided direct evidence that the ability to overtly synchronize speech motor output to an incoming speech is variable among individuals and it positively correlates with the ability to learn new words (Assaneo et al., 2019).

Several studies on native and second language learning in neurotypical developing children showed that vocabulary acquisition is strongly linked to the capacity to repeat meaningless phonological sequences (for review see Baddeley et al., 1998). Thus, higher scores in pseudoword repetition correlate with greater word-learning capacity and vocabulary acquisition over time (Gathercole, Service, Hitch, Adams, & Martin, 1999; Gathercole, Willis, Emslie, & Baddeley, 1992; Service, 1992). In the same vein, further evidence comes from studies of children with specific language impairment—a condition characterized by a delay in language development—showing that a poor non-word repetition ability is associated with worse progression in language development. This strong link between verbal repetition, as a measure of phonological processing, and language learning is also supported by the results of experimental studies showing that articulatory suppression (i.e., continuous repetition of the syllable *bla*), which block the possibility of rehearsal, significantly impairs word-learning (López-Barroso et al., 2011).

Furthermore, verbal repetition plays a fundamental role in the classification of aphasia. Aphasia, i.e., an impairment in one or more previously mastered language function after brain damage, is a disabling and frequent result after stroke. PWA usually have deficits in one or more language domains (e.g., comprehension, fluency, repetition) and, as I will present in the next section, verbal repetition is one of the three main criteria used to classify aphasia (Kertesz, 1979), this allowing to group patients with similar behavioral-brain correlate and aiding communication across clinicians. Additionally, from a neurorehabilitation perspective, the implementation of repetition and imitation-based therapies have been demonstrated to be an effective approach in language treatment of both PWA and children with developmental language disorders (Berthier et al., 2017; Duncan & Small, 2016; Lee et al., 2010). These approaches pose imitation and repetition as key elements of language therapies, based on the evidence of a shared neural network engaged during speech listening and/or observation and production. One example of this line of therapeutic approach is IMITATE (*Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effect*) (Lee et al., 2010). Complementary, *Melodic Intonation Therapy* (MIT) is also a form of repetition-based therapy, since it is thought to engage similar auditory-motor network than IMITATE, but with greater implication of the right hemisphere (Schlaug, Marchina, & Norton, 2008, 2009).

Finally, verbal repetition stands out as a critical function in neurocognitive research, used as a measure of phonological and STM/WM processing and as a gauge of neural integrity (Saur et al., 2008). Given that verbal repetition taps both the input (auditory perceptual) and output (speech) processes, its study allows a general exploration of the language network (Yoo et al., 2012). In this regard, words and meaningless legal phonological sequences (i.e.,

pseudowords) have been used in repetition tasks to assess the functionality of different components of the language network, with pseudoword repetition relying mainly on the functionality of the dorsal stream, and word (and sentence) repetition further recruiting the ventral route (Dell, Schwartz, Nozari, Faseyitan, & Branch Coslett, 2013).

### **3. Verbal repetition plays a central role in aphasia classification**

Even though most clinicians will agree that aphasia constitutes a heterogeneous clinical entity, PWA usually share some clinical similarities that allow grouping them into different aphasic profiles. In this sense, the ability to repeat words and pseudowords serves as a criterion to classify aphasias, allowing the segregation of different syndromes with topographical correlates. Thus, aphasias may be grouped in perisylvian aphasias (classical aphasias), chiefly characterized by impaired verbal repetition, and extrasylvian aphasias (or transcortical aphasias; TAs), characterized by preserved verbal repetition. Aphasias with left perisylvian involvement include Broca's, Wernicke's, conduction (CA) and global aphasias, which account for the majority of aphasia cases (Albert, 1981; Berthier, 1999). Extrasylvian aphasias include transcortical motor aphasia (TCMA), transcortical sensory aphasia (TCSA), mixed transcortical aphasia (MTCA), and anomic aphasia. While classical aphasias represent more than 80% of cases, the occurrence of TAs has been estimated to range between 4% and 20% of all aphasias (Berthier, 1999). Figure 1 depicts a summary of the main clinical features associated to each aphasia type. It is important to highlight that in some types of aphasia repetition may be one of the only available resource for communication. As well, echolalic repetition may appear as compensatory behavior aiding other language deficits (e.g., repetition deficits) as will be further discuss across the studies presented in *Block 1*.

This taxonomic classification of aphasia has not been accepted without criticism, and it has been argued that language deficits in one third of PWA cannot be accommodated with the 8 described aphasic syndromes, particularly when language evaluations are performed in the chronic stages (Berthier, Dávila, García-Casares, & Moreno-Torres, 2014; Kasselimis, Potagas, Kourtidou, & Evdokimidis, 2012). Despite its downside, this taxonomic classification remains useful as a first step in the multimodal evaluation of deficits in a PWA and mainly for clinical purposes (communication with patients and relatives, prognosis and treatment).

	APHASIA TYPE	CLINICAL PROFILE
PERISYLVIAN APHASIAS Impaired repetition	Broca	<b>Speech production:</b> nonfluent, marked by reduced production (< 50 words minute), effortful, agrammatic, abnormal prosody, often with inconsistent articulatory errors (i.e., apraxia of speech). <b>Comprehension:</b> good, in general. Impaired for grammatically complex sentences. <b>Naming:</b> impaired but better for objects than actions. <b>Others:</b> good awareness of deficits.
	Wernicke	<b>Speech production:</b> fluent but unintelligible, marked by phonemic paraphasias and neologisms, effortless, melodic, well-articulated. <b>Comprehension:</b> severely impaired, mainly in the acute phase. <b>Naming:</b> impaired (similar to speech production). <b>Others:</b> poor awareness of deficits.
	Conduction	<b>Speech production:</b> relatively spared. <b>Comprehension:</b> relatively spared. <b>Naming:</b> relatively spared. <b>Others:</b> phonemic paraphasias in all verbal domains.
	Global	<b>Speech production:</b> severely impaired. <b>Comprehension:</b> severely impaired. <b>Naming:</b> severely impaired. <b>Others:</b> frequent type in the acute post-stroke period (~ 40 % of cases). Tend to evolve to less severe types in the chronic phase.
TRANSOCORTICAL APHASIAS Preserved repetition	Motor	<b>Speech production:</b> nonfluent. Profile similar to Broca's aphasia <b>Comprehension:</b> good, in general. <b>Naming:</b> impaired. <b>Others:</b> tendency to echolalic repetition.
	Sensory	<b>Speech production:</b> fluent but unintelligible. Similar to Wernicke's aphasia profile. <b>Comprehension:</b> good, in general. <b>Naming:</b> impaired. <b>Others:</b> tendency to echolalic repetition.
	Mixed	<b>Speech production:</b> severely impaired. Similar to global aphasia profile. <b>Comprehension:</b> severely impaired. <b>Naming:</b> severely impaired. <b>Others:</b> tendency to echolalic repetition.
	Anomic	<b>Speech production:</b> relatively spared. <b>Comprehension:</b> relatively spared. <b>Naming:</b> impaired. <b>Others:</b> represents the mildest aphasia syndrome. Usually residuum of other aphasias.

Figure 1 Summary of clinical characteristics associated the different aphasias types

#### 4. Cognitive and computational approaches to verbal repetition

Cognitive models of language functioning posit that repetition is mediated by two routes: *lexical* and *non-lexical* (Hanley, Dell, Kay, & Baron, 2004; McCarthy & Warrington, 1984; Nadeau, 2001; Patterson et al., 1987). The functional architecture of dual route models commonly incorporates in the direct non-lexical route a module for acoustic-phonological conversion that mediates the input and output, which is likely to be involved in the repetition of pseudowords. The lexical route, on the other hand, supports repetition process by the

activation of a lexical entry (and its semantics components) from which the phonology is retrieved and later articulated. The distinction between lexical and non-lexical routes for repetition allows the clinical dissociation commonly observed in people with CA, (McCarthy & Warrington, 1984), in which there can be a preserved ability to repeat words and an impaired ability to repeat pseudowords, together with the production of semantic and phonological errors (see Crisp & Lambon Ralph, 2006). Further, in this line, it was also proposed that accurate language production after brain damage may be also achieved by a summation of (partial) information running through each route (“summation hypothesis”) (Hillis & Caramazza, 1991, 1995).

Dual-route models have evolved over time, from a theoretical (cognitive type) framework that characterized the major components of language (McCarthy & Warrington, 1984; Patterson et al., 1987), to modern computational models strongly influenced by neural network architecture thought to explain both normal and pathological language processing (Dell, 1986; Ueno and Lambon, Ralph, Nozari & Dell, 2013; Roelofs, 2014). One of the most influential computational instantiations of language has been devised by Dell and colleagues as the *dual-route interactive two-step* computational model. The early versions of this model used a spreading activation-like mechanism aimed to explain speech error in spontaneous speech and repetition in healthy subjects (Dell, 1986). Briefly, this model poses that the different units involved in the language network are distributed in three layers, one accounting for semantics, another for lexicon and the other for phonology. The spread of activation is continuous across layers, and it can run in any of the two directions (semantics to phonology and viceversa), depending on the task (Dell, 1986; Dell, 1988; Foygel & Dell, 2000). According to Dell, the non-lexical route involves the activation of the auditory input node, and then the activation spreads to the phoneme associated to the input, directly leading to the activation of the output phonemes. Repetition through the lexical route instead considers that the input triggers the activation of the target word and then this activation spreads to the associated phonemes in the output side. For dual-route repetition the target word and the auditory input are jointly activated, both converging and contributing to the output phoneme activation. In this proposal, semantic units are only indirectly involved in repetition (Hanley et al., 2004). This model have proved to successfully predict performance (and errors) on repetition tasks in PWA (Hanley et al., 2004; Nozari, Kittredge, Dell, & Schwartz, 2010). Importantly, information gathered from the computational *dual-route interactive two-step* models has been used to design neuroimaging studies that aimed to disentangle the brain areas and networks participating in verbal repetition (Dell, Schwartz, Nozari, Faseyitan, & Branch Coslett, 2013).



Hence, cognitive and computational models pose that verbal repetition may be achieved through either a lexical or non-lexical route, or by recruiting both routes (the summation hypothesis). In the next section, I will address in more detail the lesion correlates of repetition abilities in aphasia as well as the neural networks underpinning verbal repetition in healthy subjects.

## **5. Brain correlates of verbal repetition and its impairment**

### **5.1. Classic models of language functions with a focus on verbal repetition**

Current knowledge on the neural basis and processes sustaining verbal repetition has been strongly influenced by the work of the pioneers in the study of language. Therefore, here, I briefly present the pioneering contribution made by Carl Wernicke, Ludwig Lichtheim and Norman Geschwind to the understanding of the behavioral and neural correlates of normal and abnormal verbal repetition.

#### **5.1.1. Wernicke's work: an early connectionist proposal**

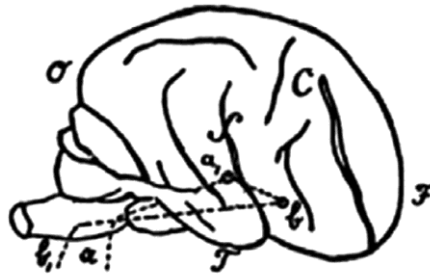
The German neuropsychiatrist Carl Wernicke (1848-1905) was one of the most influencing scholars on the study of the neurobiology of language. After Paul Broca's first description (Broca, 1861b, 1861a) of speech disturbances characterized by severe speech production and fluency impairments associated to damage to the third frontal convolution (inferior frontal gyrus, IFG), in 1874 Wernicke documented a series of complementary cases characterized by severe comprehension impairments while speech fluency was preserved but replete with neologisms and paraphasias. Post-mortem macroscopic exploration of their brains revealed lesions involving the first temporal convolution (superior temporal gyrus; STG), from which he concluded that this area was critical for language comprehension (Wernicke, 1874). His work intended to offer a model of language and language impairment with anatomical correspondence (Figure 2). Based on his model, Wernicke suggested that speech repetition was mediated by a "reflex arc". The auditory stimulus would be transferred through the acoustic nerve (a) to the sensory centre ( $a_1$ ) and from there to the motor centre and its efferent pathway concerned with speech ( $b_1$ ). Relevantly, he highlighted the importance of the subcortical white-matter connection ( $a_1b$ )—described by Meyer—that converging in the insula connected these two centres (Weiller et al., 2011; Fontana, 2019). Wernicke went on suggesting that this was the mechanism by which children acquired language by imitation of what they heard, and further speculated that another pathway linked to meaning may be used for language production in later stages of development.

Less known is the fact that Wernicke not just highlighted the existence of a connection between the currently known as Broca's and Wernicke's areas —*direct route*— but also between the “word concept centre” and the “sound image centre” —*indirect route*. These connections probably corresponded with the arcuate fasciculus (AF) or superior longitudinal fasciculus as direct route; and the extreme capsule (overlapping with the inferior longitudinal fasciculus [ILF] and inferior fronto-occipital fasciculus [IFOF]) and the uncinata fasciculus (UF) as indirect route (Weiller et al., 2011). This fits well with the most accepted contemporary model of language (described in detail in a next section) which states that language functions are sustained by two processing streams, the dorsal and the ventral (Hickok & Poeppel, 2004, 2007; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011). However, further elaborations of Wernicke's model (e.g., Geschwind, 1965) led to misinterpretation regarding the tracts pointed by Wernicke as relevant for language functions, limiting these to the AF (Weiller et al., 2011).

Applying his language model, Wernicke predicted the occurrence of different profiles of language deficits associated to different locations of brain lesions, including the “sound image centre” ( $a_1$ ), the “motor image centre” (b), and the disruption of the connection between these centres ( $a_1b$ ). He stated that the latest would result in a syndrome termed *leitungsaphasia*, or CA. Later, Goldstein (1948) argued that CA was not only the result of lesions affecting the connection between language centres, but it may also be caused by cortical disruption, renaming the syndrome as central aphasia (Anderson et al., 1999; Goldstein, 1948). In Wernicke's initial postulation, the hallmark symptom of CA was the presence of paraphasias in speech production, rather than repetition deficits. However, in a later work, Wernicke (1906) revised and further developed the syndrome of CA taking into consideration Lichtheim's model (see below) and introduced a new node labelled “word concept centre” (“Wortbegriff”) (Weiller et al., 2011; Wernicke, 1906). In that monograph, Wernicke accepted impaired repetition of nonsense words and paraphasias as key symptoms of CA resulting from the disruption of the  $a_1b$  connection. Interestingly, he made a distinction between the repetition of pseudowords, which could be repeated only through the  $a_1b$  connection, and words. For the latest, he stated that after a disruption of the main connection “...it should still be possible to repeat at command words which have a meaning” (Wernicke, 1906). Later, Goldstein pointed out that the successive approximations to the target word by means of repetitive phonological self-corrections (*conduite d'approche*) were also a distinctive symptom of CA (Anderson et al., 1999; Goldstein, 1948).

To sum up, several contributions of Wernicke's work can be highlighted: (1) he developed the first model of language processing, describing neural “centres” critical for

language functions which could correspond to what nowadays is known as *hubs*; (2) he conceptualized language as a function that emerge from the interaction of these critical centers; (3) he emphasized the importance of white-matter connections; (4) he characterized CA syndrome and distinguished the repetition of meaningfully versus meaningless phoneme strings (i.e., words vs pseudowords); and lastly (5) he formulated a clinical classification of aphasia describing three types (Broca's, Wernicke's, and CA), with different neural correlates.

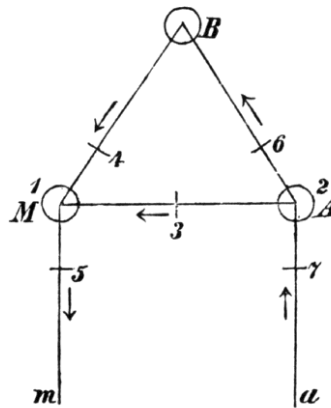


**Figure 2.** Original Wernicke's schema of the language network supporting speech production, comprehension and repetition (1874). Two main centers are depicted: “sound image centre” (a<sub>1</sub>) and “motor image centre” (b). Both centers are connected by a subcortical pathway running through the insular cortex (a<sub>1</sub>b). F, T and O refers to frontal, temporal and occipital lobe, respectively; S: sylvian fissure; a: acoustic nerve; b<sub>1</sub>: exit of the centrifugal pathway subserving articulation. Note that this diagram shows the right hemisphere.

### 5.1.2. Lichtheim's house: commissures and new aphasic syndromes

A decade after Wernicke's initial formulation, the polish Ludwig Lichtheim (1845-1928) further extended his proposal by staging a theoretical prediction of seven aphasic syndromes, presenting the iconic schematic drawing currently known as Lichtheim's house (Figure 3). In his proposal, Lichtheim (1885) described three main nodes: a “motor language centre” (M) corresponding with Broca's area, a “sensory language centre” (A) corresponding with Wernicke's area, and suggested a new one which he termed the “concepts centre” (B → *Begriffe*). Several distinctive functions have been suggested by Lichtheim for the connection between these nodes, being the “A-B-M” path involved in volitional speech, while the “A-M” connection was proposed to support automatic (or “reflex”) speech. It is worth noting that this last path corresponds with the a<sub>1</sub>b connection in Wernicke's proposal (i.e., direct route). Lichtheim preserved the original formulation of Wernicke's (1874) and postulated that the disruption of “A-M” connection would result in CA. As well, he supported that the hallmark feature of CA was the presence of paraphasias and not repetition deficits, since this could be reached through the indirect connection “A-B-M”. More importantly, in this model

Lichtheim described two new type of aphasias which combined impaired language abilities (i.e., comprehension, production, or both) with preservation of verbal repetition skills, named *commissural aphasias* (Berthier, 1999; Henderson, 1992). The term TA was later coined by Wernicke (Berthier, 1999) and, since then, the original Lichtheim's terms *inner commissural aphasia* and *inner commissural word-deafness* were replaced for TCMA and TCSA, respectively. As Figure 3 depicts, Lichtheim's proposal considered seven putative disruptions, each causing a distinctive clinical picture.



**Figure 3.** Lichtheim's house: schema of language organization and language disruption. This diagram illustrates different aphasias profiles associated to different lesion locations. In current terminology, he proposed that a lesion in "A" would cause a Wernicke's aphasia, lesion in "M" would result in Broca's aphasia, disruption of the connection "3" will be associated with a profile of conduction aphasia, disruption of the connection "6" would result in transcortical sensory aphasia, and damage of "4" would derive in transcortical motor aphasia. Finally, the interruption of the connections "5" and "7" would cause sensory and motor deficits rather than aphasic symptoms.

Therefore, the main contribution of Lichtheim was the description and characterization of new aphasias types (Eling, 2011) based on the disruption of the anatomical connections between the proposed language hubs. He described two new aphasias (TCMA and TCSA) and predicted the combination of both syndromes producing what is currently classified as MTCA (Berthier, 1999). Lichtheim introduced the conceptual center (B) and the connection between this and the other two centers (i.e., A and M), opening the possibility of disconnection in several points of the language system which would result in distinctive aphasia profiles. Another important contribution made by Lichtheim was that he considered that the "concept centre" was a distributed set of radiated connections along the cerebral cortex rather than located at one spot. This could be the first conceptualization that the "semantic system" is widely distributed in the brain. In fact, the connections A-B and B-M would represent the convergence of different tracts in two major speech centers.

It is noteworthy that three convergent discoveries ensued in nearly 20 years. First, Broca described a brain area crucial for language production (named by Wernicke “motor image centre”); second, Wernicke’s introduced the “auditory image center” and the connection linking the motor and the auditory image centers. From this description, Wernicke predicted three aphasia types; and third, Lichtheim expanded the model, highlighting the connections (“commissures”) linking the centers previously discovered by Broca and Wernicke (Henderson, 1992). In short, the Wernicke-Lichtheim model is considered a milestone in the study of the neurobiology of language, providing an explanation of the aphasic syndromes, yet without detailed anatomical correspondence due to the limitations of XIX century’s methods.

### **5.1.3. Geschwind: the disconnection account**

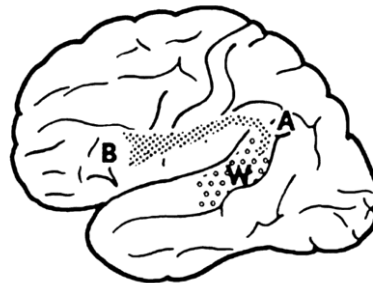
In the 60s, the behavioral neurologist from Boston Norman Geschwind (1926-1984) reintroduced and further developed the Wernicke-Lichtheim model in the light of the twentieth century’s emerging neuroscience. He suggested that the white matter pathway proposed by Wernicke to link the posterior “sound images centre” to the “motor images centre” is the AF and formulated that CA may result from the disruption of this tract (Figure 4). With this, he outlined a specific anatomical structure that fitted with the proposal of Wernicke (1874) and with the theoretical taxonomy of Lichtheim (1885). Importantly, Geschwind broadened the concept of disconnection syndrome introduced by Wernicke, which was limited to lesions involving white matter tracts that disconnected cortical regions, to the involvement of cortical areas that had the same effect. This new view, was further extended to the understanding of the neural basis of the CA syndrome, suggesting that CA could result from either white-matter damage or involvement of the overlying cortical tissue that disconnected Broca’s and Wernicke’s areas. As well, he advocated that Wernicke’s aphasia could also be understood as a disconnection syndrome. In this case, both lesions in Wernicke’s area and the connection from this to the angular gyrus (AG) could cause this type of aphasia. Geschwind posited that the AG may play an important role in language processing, acting as a “cross-modal association” area between hearing, vision and touch. This means that a given name would pass through Wernicke’s area then this information will be transferred to the AG and this area will eventually trigger activation of the name’s associated features (i.e., shape, smell) in other cortical areas (Catani & Mesulam, 2008).

Further, it is noteworthy that Geschwind (Geschwind, Quadfasel, & Segarra, 1968) revived the idea of *isolation of speech area* early introduced by Goldstein (1917), to explain a rare type of aphasia (i.e., MTCA). Goldstein (1917) devised that severe impairment in verbal production and auditory comprehension with preserved, yet echolalic, repetition

should have lesions placed outside the “central” perisylvian language area (e.g., speech area). In his view, these lesions were “peripheral” and could not only account for explaining major language deficits, but also were well-suited for “isolating” the anatomically spared left speech area, which by being out of control of superior cortical centers (frontal and parietal), released a poorly monitored echolalic repetition.

### Final comments

The ground-breaking contributions of the pioneers is unquestionable. They set the basis of the study of the neurobiology of language, outlined aphasic syndromes posing repetition as one of the major functions, and enlightening the subsequent research on the field. Yet, it is currently accepted that classical models need to be updated in the light of current evidence (Poepfel, Emmorey, Hickok, & Pylkkänen, 2012). The development of neuroimaging-techniques had promoted a colossal expansion of the knowledge of the neural basis of language and its relation to language disturbances, leading to the emergence of new proposals based on stronger empirical evidence, thus overcoming one of the main drawbacks of the old proposals (Eling, 2011). Fewer updates have been made regarding aphasias classification. After Lichtheim (1885), the clinical profile proposed for the different aphasias was widely accepted (Albert, 1981), although much more clinical evidence was gathered. In the next sections I will review modern evidence of the neural correlates of the different aphasia’s types, present current models of language processing, and knowledge of the brain networks supporting verbal repetition derived from neuroimaging studies.



**Figure 4.** Original Geschwind’s schema of the language network. B, Broca’s area, which lies anterior to the lower end of the motor cortex; W (open circles), Wernicke’s area; A (closed circles), arcuate fasciculus which connects Wernicke’s to Broca’s area. Figure and caption from Geschwind, 1970.

#### 5.1.4. Modern evidence of a classical view: neural correlates of aphasia

In the last decades, some of the early claims regarding brain-language relationships have been challenged, for instance, by re-examination of Broca’s patients brain (Dronkers et al., 2007; Thiebaut de Schotten et al., 2015), or by cases of Wernicke’s aphasia without

damage to Wernicke's area (Ogar et al., 2011). In fact, great efforts have been placed in exploring the correspondence of aphasic syndromes and lesion location in the light of modern neuroimaging techniques. In this sense, the voxel-lesion symptom mapping (VLSM) approach—an analysis method of structural MRI that provide a measure of how strongly a lesion in a given voxel predicts performance in a task (Bates et al., 2003)—has provided important advances. Using this approach, Henseler, Regenbrecht, and Obrig (2014) have explored the lesion location associated to different aphasic syndromes in a sample of 102 chronic aphasics, and their results showed a clear distinction in the anatomical areas involved in Wernicke's and Broca's aphasia, with minimal overlap between them. Broca's aphasia profile was found to be associated with lesions affecting the IFG, IC, surrounding white matter and basal ganglia of the left hemisphere, while Wernicke's aphasia was associated to posterior lesions involving the temporal gyrus (STG, middle temporal gyrus [MTG], and inferior temporal gyrus [ITG]), the temporo-parietal junction, and the temporo-occipital regions (Figure 5, panel A).

Similarly, another study with a large aphasic sample ( $n = 98$ , chronic stage) identified the lesion locations that better predict the four classical aphasic syndromes (Yourganov, Smith, Fridriksson, & Rorden, 2015). In agreement with previous study, lesions affecting the IFG and the AF (anterior and long segments) better predicted Broca's aphasia, whereas damage to the AG and Heschl's gyrus predicted Wernicke's aphasia. CA was associated to lesions encompassing the posterior segment of the AF and Heschl's gyrus (Yourganov et al., 2015) (Figure 5, panel B). In a more specific way, another study suggested that disruption of the anterior segment of the AF is associated to the emergence of a Broca-like CA, while reduction in the integrity of the left posterior segment of the AF is associated with Wernicke-like CA (Song et al., 2011). Yet, the critical components damaged in cases of CA and, therefore, critical structures for repetition ability, are still under debate. Given its relevance for the present dissertation, this issue is further discussed in a next section. Lastly, in Yourganov and colleagues' study (2015), global aphasia was predicted by involvement of several components of the fronto-temporal network including the AF (Yourganov et al., 2015), while no brain areas were predictive of anomic aphasia (Figure 5, panel B), suggesting that this last one has non-localizing value.

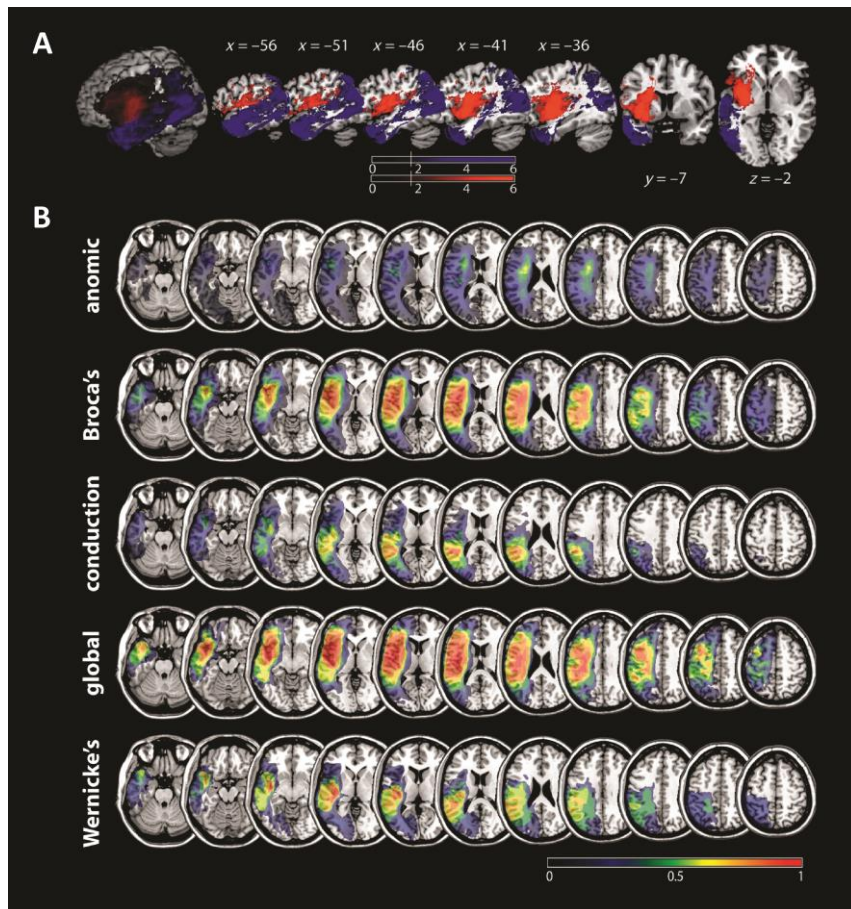
Regarding aphasias with preserved repetition, given its lower prevalence, current knowledge mostly came from single cases and case series studies (but see Berthier et al., 1991 for a group study). These aphasias are usually caused by lesions affecting borderzone vascular territories either between the anterior cerebral artery and middle cerebral artery, in the case of TCMAAs, or between the later and the posterior cerebral artery in TCSAs (Cauquil-

Michon, Flamand-Roze, & Denier, 2011). Generally, TCMA cases are associated to damage in left frontal areas, supplementary motor area (SMA), and deep white matter, which may disrupt the connections between SMA and perisylvian areas involved in speech production (Cauquil-Michon et al., 2011; Freedman, Alexander, & Naeser, 1984). Further, TCSA was reported after lesions affecting a variety of regions including lateral thalamus, STG, temporo-parietal-occipital junction and temporo-occipital area. Thus, comprehension deficits associated to TCSA may be explained by disconnection between the auditory (or visual) areas and semantic areas (Cauquil-Michon et al., 2011). In these aphasic syndromes, preservation of repetition is normally associated with sparing of the left perisylvian network supporting this function (Berthier, 1999), however there are several cases of aphasia with preserved repetition abilities and extensive damage to the left perisylvian area. In these cases, repetition preservation (or its recovery) may be sustained by the recruitment of preserved right hemisphere areas (Berthier et al., 1991; Berthier, 1999). Yet, the time course for repetition recovery may be variable, with some studies describing a rapid recovery after brain damage (Berthier et al., 1991; Tanabe et al., 1987) and others describing progressively recovery that may continue even after several years (Pulvermüller & Schönle, 1993).

Since language is grounded on a complex and segregated neural network (Mesulam, 1990), a focal lesion may cause local and distant negative effects (diaschisis) (Carrera & Tognoni, 2014). In agreement with this idea, it has been proposed that language disturbances are better characterized by the disruption of cortical and functional networks rather than by local damage (Fridriksson et al., 2018; Klingbeil, Wawrzyniak, Stockert, & Saur, 2019). Thus, by using functional connectivity analytical approaches (e.g., resting state functional connectivity) several studies have provided evidence on the connectivity profile seen in PWA. Altogether, these data suggest that a decrease of interhemispheric and intrahemispheric resting state functional connectivity correlates with language deficits (for a review see Klingbeil, Wawrzyniak, Stockert, & Saur, 2019). Nevertheless, this is an emerging approach and no association between connectivity profiles and aphasic types has been delineated yet.

Summarizing, the evidence presented above shows that despite the heterogeneity on lesion location among the same aphasic syndrome (see figure 5, panel B), there are within-group similarities in the lesions' distribution that allows differentiating one aphasia type from others, thus, providing evidence in favor of a brain/language correspondence. However, as it could be inferred, this relationship is far more complex and variable across individuals than the proposed by early scholars.





**Figure 5.** Lesions associated to different aphasic syndromes. **(A)** VLSM-maps showing lesions significantly associated with Broca's aphasia (red) and Wernicke's aphasia (blue). All voxels shown exceeded the critical threshold for significance (indicated by the white line in the colour bars,  $p < .05$  FDR-corrected). Lighter colors reflect increasing Z-scores. Numbers indicate MNI coordinates. Figure and figure legend adapted from Henseler et al., 2014. **(B)** Lesion overlap across patients with each aphasia type. The color bar indicates the proportion of patients with damage in a given voxel. A voxel with overlap = 1 indicates that this voxel was lesioned in all patients. Figure and figure legend adapted from Yourganov et al., 2015

## 5.2. Contemporary models of language functions with a focus on verbal repetition

Echoing back words, pseudowords or sentences involves the mapping between phonological relevant content and the motor pattern required for their pronunciation. Although not required, repeating a stimulus also involves automatic imitation of auditory parameters (Kappes et al., 2009) and visual signals through action observation (Iacoboni et al., 1999; Kohler et al., 2002). Thus, given that both imitation and auditory-motor transformation are relevant for speech repetition, in this section I describe the mirror neuron

system in the human brain and the neurocognitive dual-stream model as a brain conceptualization of the repetition process.

### **5.2.1. Audio-visual mirror neuron system**

The *motor theory of speech perception* highlights the importance of motor gestures in speech perception (Liberman and Mattingly, 1985). Accordingly, not only the sounds *per se* are essential for speech perception, but further the articulatory gestures associated with them. During perception, the sounds of speech are directly mapped onto the articulatory-based representations, which in addition to allow the reproduction of the just heard sound, aids listeners' understanding. More recently, the description of the mirror neuron system brought back this idea. The mirror neuron system is composed of a group of neurons that become active when executing a goal-directed action but also when observing the action (Giacomo Rizzolatti & Craighero, 2004; Giacomo Rizzolatti, Fogassi, & Gallese, 2001). One of the first neuroimaging evidence of the mirror neuron system in humans comes from a positron emission tomography experiment showing that both the observation of an action (i.e., grasp an object) and its execution induced activation in the STG and MTG, and the caudal portion of the IFG (BA45) (Rizzolatti et al., 1996). In the language domain, using transcranial magnetic stimulation (TMS) recordings, it was demonstrated that passive listening of words induces an increase of activation in language motor centers (Fadiga, Craighero, Buccino, & Rizzolatti, 2002), providing evidence for a link between speech perception and motor actions. Subsequently, several functional neuroimaging experiments have explored the brain areas that respond to both speech perception and production. Findings suggest that areas with common response mainly encompasses the bilateral posterior STG, inferior parietal cortex (IPC), premotor cortex (PMC) and IFG (Buchsbaum, Hickok, & Humphries, 2001; Mashal, Solodkin, Dick, Chen, & Small, 2012), among other areas involved in planning and execution of speech.

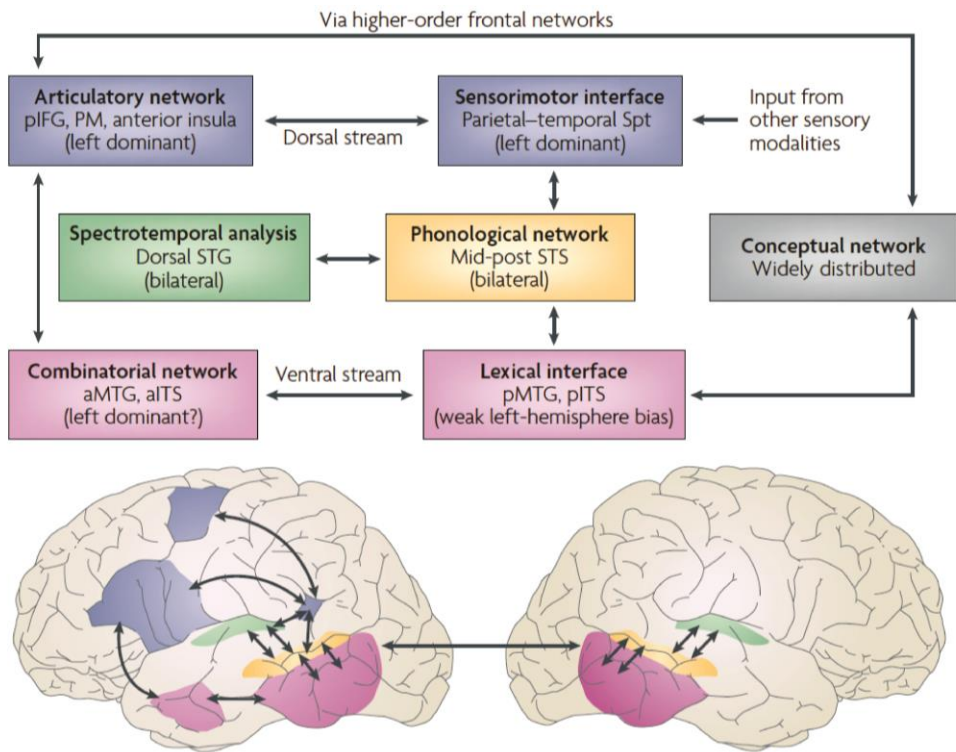
### **5.2.2. The dual-stream model**

The dual stream model, developed as a language equivalence for the visual “what” and “where” pathways (Ungerleider & Haxby, 1994), is the most extended modern neurocognitive model of language processing. This model, intended to link previous cognitive approaches with the motor control theory (Hickok & Poeppel, 2004, 2007), highlights the importance of the auditory-motor network for speech perception and production. According to this, the language network is organized in two functional and anatomical segregated streams, named dorsal and ventral.

Hickok and Poeppel (2004, 2007) posit that the dorsal stream is mainly involved in auditory-motor integration, that is, the translation of auditory stimuli into the motor pattern that allows its pronunciation. Thereby, it constitutes the main stream supporting verbal repetition, especially of words lacking meaning (e.g., pseudowords) (Saur et al., 2008). Further important functions associated to the dorsal stream are online speech monitoring and errors correction (Hickok et al., 2011; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009), new vocabulary acquisition and phonological short term memory (Hickok & Poeppel, 2007; Lopez-Barroso et al., 2013; López-Barroso et al., 2015). On the other hand, the ventral stream mainly supports lexico-semantic processing, that is, the access to the memory trace that associate the word-form to its meaning, which may also mediate repetition of words and sentences (Hickok & Poeppel, 2007).

According to this proposal, early stages of auditory processing involve the posterior portion of the bilateral STG, and from this area two processing streams emerge: one running dorsally and one ventrally, being the dorsal left-lateralized, and the ventral bilaterally distributed (Catani and Mesulam, 2008). The dorsal stream projects from STG to the IPC, and from there to frontal areas involved in articulatory-motor processes including the IFG, PMC and IC. Moreover, the ventral stream projects from the STG to the posterior MTG and ITG. These areas are thought to be a lexical interface, linking lexical stimuli with their semantic representations (Hickok & Poeppel, 2007). Then, information is transferred to the anterior temporal gyrus—which may have a combinatory role for lexical-semantic and sentence-level processes (syntactic and semantic integration)—and, after to the IFG, part of the dorsal stream according to this proposal. Figure 6 depicts the functional and anatomical features of the model as proposed by Hickok and Poppel (2007). This model has been supported by hundreds of neuroimaging studies (for a review of functional studies see Price, 2012) targeting healthy and brain-damaged patients (Fridriksson et al., 2016; Saur et al., 2008).

As a final comment, it is noteworthy that the cortical areas encompassing the audio-visual mirror neuron system and areas subserving the dorsal stream are tightly intertwined and overlap at some parts. This may explain, for instance, the findings of greater improvement of spontaneous speech with audio-visual feedback than audio-only feedback observed in some PWA (Fridriksson et al., 2012), suggesting that combined auditory and visual signals may induce simultaneous engagement of these interrelated and overlapping left networks, thus aiding speech production.



**Figure 6.** Functional anatomy of the dual-stream model of language processing proposed by Hickok & Poeppel. IFG: inferior frontal gyrus; Spt: Sylvian–parietal–temporal; STG: superior temporal gyrus; STS: superior temporal sulcus; MTG: middle temporal gyrus; ITS: inferior temporal sulcus; p: posterior; a: anterior. Figure from Hickok & Poeppel (2007).

### 5.2.3. Integrative models: verbal repetition and phonological short-term/working memory

Behavioral assessment of verbal repetition and verbal working memory (i.e., repetition of words, sentences or word series), and the neural network supporting these functions, overlap to a great extent (Baldo, Katseff, & Dronkers, 2012; Salis, Kelly, & Code, 2015). Nevertheless, the study of language and memory have traditionally evolved as separate fields, thus verbal repetition and phonological rehearsal have been mostly studied as independent functions.

Verbal repetition is a language function that inevitably implies the maintenance of phonological information, at least for a very short period (Hickok & Poeppel, 2007; Majerus, 2013). At the same time, models of WM (Baddeley & Hitch, 1974; Cowan, 1999) have proposed subvocal verbal repetition (i.e., rehearsal) as a mechanism needed to refresh the information and avoid memory decay, suggesting that these two functions are intimately linked. In fact, in many cases both processes are difficult to segregate. For instance, in some abnormal repetition conditions, such as echolalia –a frequent symptom of TAs–, the recurrent

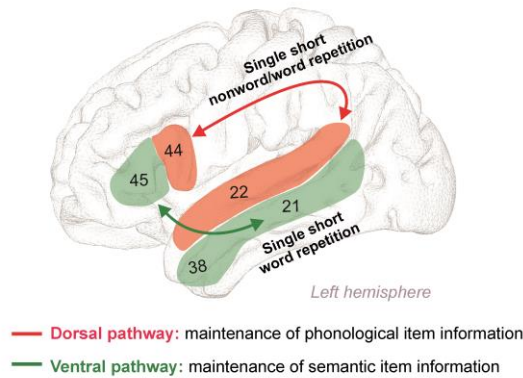
repetition of verbal material may play, in some patients, the role of “overt rehearsal” that compensate WM difficulties. The functionality of echolalia will be deeply discussed in Studies 2 and 3 of the present dissertation. Likewise, CA –which is characterized by deficits in verbal repetition and phonological STM/WM– may serve to further exemplify the existent link between repetition and WM (Kohn, 1992; Shallice & Warrington, 1977).

Recently, neurocognitive integrative models of verbal repetition and STM/WM have been formulated. In this line, Buchsbaum & D’Esposito (2019) proposed that phonological maintenance rely on auditory-motor processes undergoing in the language dorsal stream supporting verbal repetition. According to this proposal, three are the main components supporting phonological STM and verbal repetition: (1) the auditory areas involving the STG; (2) the auditory-motor interface –a mechanism that process auditory information and transforms it into an articulatory code that guides motor action; and (3) the articulatory motor areas placed in the IFG. In a simplified manner, this approach poses that a continuous flow of information between auditory and motor areas, mediated by the auditory-motor interface, allows to maintain phonological information active. This account rejects the existence of a “container” that temporarily store phonological sequences (as proposed by Baddeley, 1992; Baddeley & Hitch, 1974); rather STM is understand as a process that emerges from the language network supporting auditory-motor integration (i.e., dorsal stream).

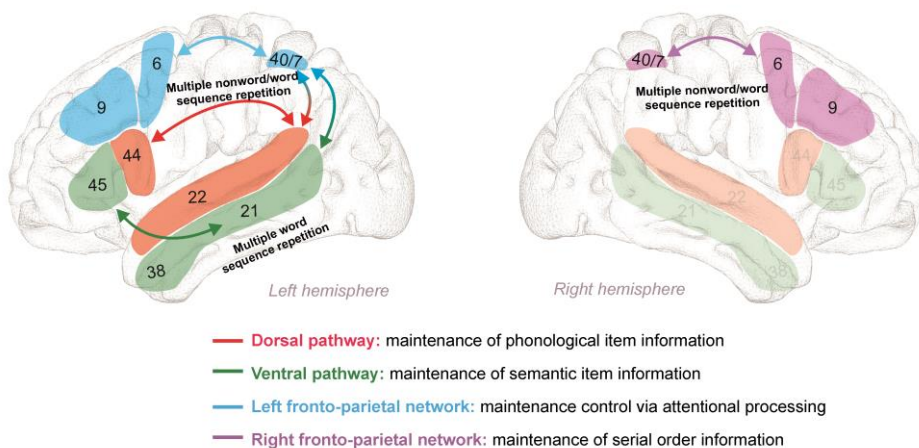
Similarly, Majerus (2013) possess a model that abandons the existence of a specific dedicated storage for verbal sequences. Instead, the model proposes that the maintenance of phonological and semantic information is supported by the dorsal and ventral language streams, respectively. Accordingly, verbal information is maintained active by reactivation and rehearsal, eventually allowing it repetition. Relevantly, the author differentiates between repetition of single items (words and short pseudowords) and word series. Thus, whereas repetition of single items is supported by the above-mentioned language pathways, repetition of word series and long pseudowords, which requires higher attentional load, is supported by a fronto-parietal network that aids attentional control and serial order maintenance. Figure 7 depicts areas supporting the repetition of short items and sentences, as proposed by Majerus (2013). In short, attempts to understand phonological STM within the current knowledge of brain functioning suggest that this function emerges from recurrent excitatory loops of auditory-motor areas within the language pathways and, in some occasions, with further participation of areas supporting general-domain processes.

**A**

## Brain networks for single word and nonword repetition

**B**

## Brain networks for multiple word and nonword sequence repetition



**Figure 7.** Networks supporting phonological maintenance processes during repetition. **(A)** Maintenance of phonological sequences during short pseudowords repetition is supported by the dorsal language pathway linking the superior temporal gyrus with the posterior inferior frontal gyrus. Maintenance of single words during repetition is also sustained by the dorsal pathway but with additional support of the ventral language pathway, linking the middle temporal cortex with the anterior inferior frontal gyrus. This reflects the temporal activation of the semantic representation associated with the to-be repeated item. The frontal areas reached by each pathway are proposed to preclude from possible phonological and semantic interferences. **(B)** Maintenance of multiples pseudowords and words for repetition involves a bilateral fronto-parietal network implicated in domain-general attentional and serial ordering processes, in addition to the left dorsal and ventral language pathways which participate in the maintenance of phonological and semantic information, respectively. The left fronto-parietal network, linking the intraparietal sulcus with the superior and middle prefrontal cortices, is proposed to support the maintenance of multiples verbal stimuli by focusing attentional resources on the representation temporarily activated in the dorsal and ventral pathways. In the right hemisphere, the fronto-parietal network is proposed to support the maintenance of serial order information, which is needed to withhold the occurrence order of words within a list or sentence, and of phonemes/syllables within a novel word. The numbers indicate Brodmann areas. Figure and figure legend based on Majerus et al. (2013).

## **6. Neural basis of verbal repetition: modern evidence**

The current knowledge on the neural basis of verbal repetition is the result of multiple studies based on different populations including healthy subjects, patients undergoing awake brain surgery, and PWA. Likely, different techniques have been employed such as structural and functional magnetic imaging (fMRI), magnetoencephalography (MEG) and electrocorticography (ECoG), each providing unique insights on the network supporting verbal repetition. For instance, fMRI-based evidence from healthy subjects has the potential to inform on the areas showing increased activation during the performance of a given task, while using methods based on the correlation between lesion and symptoms can reveal areas that need to be spared for successful performance (Fridriksson et al., 2016). Further, while fMRI has a good spatial resolution, MEG and ECoG have high temporal resolution (Babiloni, Pizzella, Gratta, Ferretti, & Romani, 2009). Thus, besides their relevant contribution to the localization of important neural areas, these two last methods have critically contributed to delineate the time course of cortical involvement during verbal repetition tasks.

In this section I will review the current evidence on the neural correlates of verbal repetition, taking into account important variables that may influence results such as type of the to-be repeated material (single words vs sentences, words vs pseudowords and so on), as well as the articulatory involvement during the task (cover vs overt).

### **6.1. Evidence from healthy subjects and intraoperative recordings**

Findings from studies based on healthy subjects and intraoperative recordings in patients with tumors or treatment-refractory epilepsy evidenced that verbal repetition involves a large bilateral network that encompasses perceptive and production speech areas, as well as several white matter tracts connecting these areas. Verbal repetition of words and pseudoword commonly induce strong activation over a bilateral temporo-frontal network encompassing superior/middle temporal areas as well as the middle/inferior frontal gyri, together with primary motor and PMC (Hartwigsen et al., 2013; Saur et al., 2008; Yoo et al., 2012). Although similar regions are usually involved in the repetition of both type of stimuli, pseudowords tend to induce greater activation in the left temporo-frontal network than words including STG, IFG, anterior IC (Palomar-García, Sanjuán, Bueichekú, Ventura-Campos, & Ávila, 2017; Saur et al., 2008) and PMC, as well as the bilateral SMA (Hartwigsen et al., 2013), while words seem to involve to a greater degree the posterior areas of the left STG, including the AG, than pseudowords (Palomar-García et al., 2017; Yoo et al., 2012).

To perform a fine-grain dissection of the neural network components supporting verbal repetition in relation with the different sub-processes involved, Hope and colleagues (2014) ran a complex within-subject fMRI study with 16 different conditions. This methodology allowed the authors to dissect the brain regions supporting 10 sublevel computations carried out during the repetition of words. The factors considered were: (1) effect of stimuli modality (auditory vs visual); (2) phonological cues (presence vs absence); (3) familiar semantic content (presence vs absence); (4) speech production (covert vs overt).

The results revealed a complex neural network involving several areas, with different regions associated to each of the sub-processes. It is to note that all the contrasts used in this study were active (i.e., task related), meaning that results do not reveal areas “active” during the task; rather they depict the areas with significantly greater involvement in one task compared to other. Specifically, greater activation for auditory than visual processing was depicted in the bilateral STG (L1 and L9 in table 1). Further, results did not yield any area to be specifically associated to phonological processing of auditory stimuli (L2 in table 1), yet, the analyses revealed areas that were commonly active for auditory and visual phonological stimuli including the left superior temporal sulcus and left posterior putamen (L3 in Table 1). Increased activity in the left ventral PMC and the anterior putamen was associated to motor execution of speech influenced by sublexical phonological processing (L5 in Table 1), while activity within the IFG pars orbitalis (boundary with pars triangularis) was found during covert speech (i.e., condition without motor component) (L4 in Table 1). Semantic content effect disclosed significant involvement of the left IFG pars orbitalis (ventral portion) (L6 y L7 in Table 1) and in the left posterior MTG extending into the AG, hippocampus, and right cerebellum (L7 in Table 1). Also, overt in comparison to covert speech was associated with activation in several areas including the bilateral SMA, anterior cingulate gyrus, precentral gyri, IC, putamen, temporal lobe, and cerebellum (L8 in Table 1).

Further regions associated with each of the 10 sub-processing levels proposed by the authors to be involved in auditory word repetition are specified in Table 1 (Hope et al., 2014). In short, the study by Hope and co-workers revealed that verbal repetition depends on the concerted action of several brain regions in charge of different subprocesses.



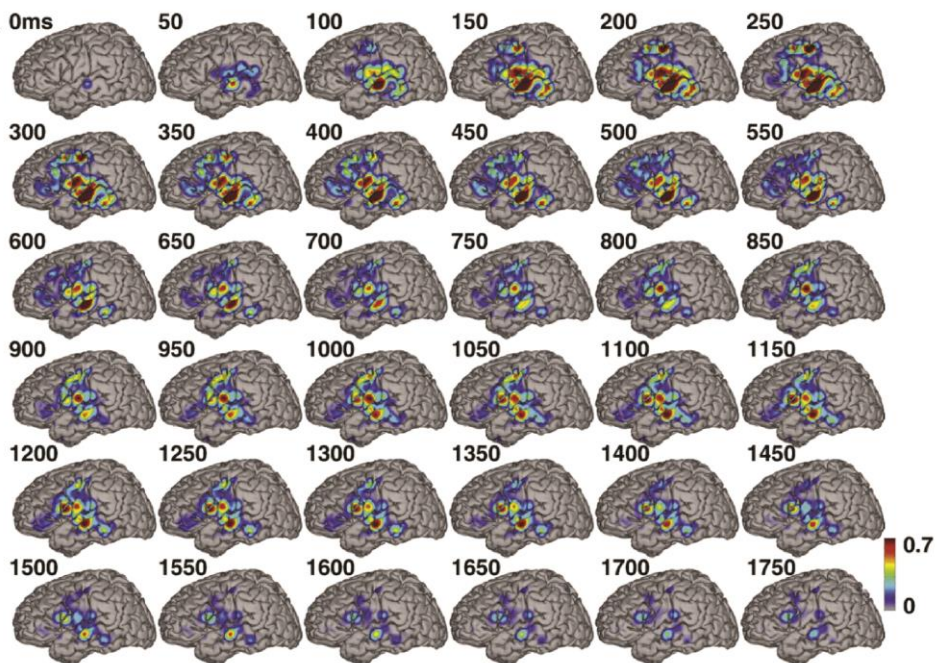
**Table 1.** Processes associated to word repetition and relevant brain areas supporting them. Table based on Hope et al. (2014).

Levels of processing in word repetition	Description	Area associated
L1. Auditory processing of all input	Acoustic processing common to all types of sounds including speech	Bilateral STG, including Heschl's gyri and planum temporale
L2. Auditory phonological input	Speech enhanced acoustic processing, possibly resulting from the complexity of speech sounds	No-significant areas
L3. Sublexical phonological inputs	Sublexical processing of auditory & visual inputs that can be recoded into articulation	Left STS, left p-putamen
L4. Covert articulation	Articulatory processing/preparation during silent tasks, i.e., prior to overt production	Left pOrb/pTri
L5. Phonological inputs on overt speech	The influence of sublexical phonological associations on overt articulation	Left v-PM and Left a-putamen
L6. Semantic access/associations	Recognizing the meaning of words, even when they don't have to be reproduced	Left pOrb
L7. Semantic input to articulation	Retrieving phonology/articulatory associations from semantic processing	Left pMTG, angular, hippocampus, right CB, left FO, pOrb, pTri, IFS
L8. Motor control of overt speech	Motor execution of speech output (orofacial, larynx, breathing)	Precentral, postcentral, CB, a-INS, v-putamen, amygdala, Tp, pTri, SMA, ACC
L9. Auditory feedback	Auditory processing of sounds produced during speech production	Bilateral STG, including Heschl's gyri and planum temporale
L10. Domain general processing	Processing that is independent of stimuli or the effector used to respond (e.g., fingers or mouth)	ACC, SMA, pre-SMA, Left d-pOp/dPM, vPM, aINS-d, SMG, lateral CB

p: posterior; a: anterior; d: dorsal; v: ventral; STS: superior temporal sulcus; Orb: pars orbitalis; Tri: pars triangularis; PM: premotor; MTG: middle temporal gyrus; CB: cerebellum; FO: frontal operculum; Tp: temporal pole; IFS: inferior frontal sulcus; SMA: supplementary motor area; SMG: Supramarginal gyrus; ACC: anterior cingulate cortex; INS: insula.

In a complementary way, studies based on ECoG recording further informed on the areas associated to speech repetition as well as the time-dynamics of the underlying cortical activation. At early stages, overt repetition is accompanied by activation of posterior MTG and STG (beginning at 0 ms) which is related to acoustic processing. After, the perisylvian area, including PMC, becomes active, probably associated to speech perception/recognition and, later, the amplitude and spatial extent decrease until the 700 ms, time by which a second increase, related to production is initiated. At this stage, the activation in the perisylvian area increases, comprising primary motor areas, PMC, and temporal areas (peak at 1200 ms), likely related to motor planning of speech and speech processing of the spoken word (Pei et

al., 2011) (Figure 8). Covert auditory repetition induced a similar pattern in the early acoustic processing phase, but as expected, with lower activation over primary motor cortex as well as over posterior STG and MTG (Pei et al., 2011). Activation associated to stimuli processing appears later for visually presented stimuli (Leuthardt et al., 2012; Pei et al., 2011). Interestingly, ECoG recordings during repetition tasks suggest that most of the repetition errors are triggered by stimulation of the posterior STG and MTG. More precisely, phonological paraphasias and perseverations (e.g., repetition of a previous response) were induced by inhibitory stimulation of different portions of the posterior STG and supramarginal gyrus (SMG), while neologisms are triggered by inhibitory stimulation of the anterior STG. Further, motor errors (e.g., distorted speech) are associated to functioning disruption of primary motor areas and ventral post-central gyrus and less often to the STG and IFG (Leonard, Cai, Babiak, Ren, & Chang, 2019). As a limitation, note that stimulation studies using ECoG recordings frequently do not consider the contribution of the right hemisphere to speech repetition, since the electrode grid is generally placed on the left hemisphere.



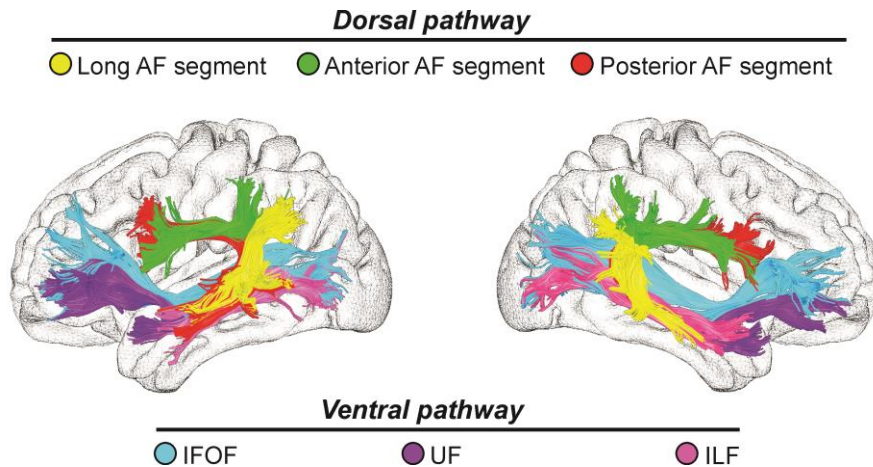
**Figure 8.** Spatiotemporal dynamics of brain activation associated to overt word repetition as measured with electrocorticography over nine epileptic patients. Color-bar depicts coefficient of determination ( $r^2$ ), which indicates statistical differences in electrocorticography amplitude between overt repetition compared to rest. Numbers indicate time since stimuli onset in ms. The average measures for all participant reported in Pei et al., 2011 is represented. Figure adapted from Pei et al., 2011.

## White matter tracts involved in verbal repetition

Fitting dual stream model of language processing (e.g., Hickok and Poeppel 2007), key areas for word and pseudoword repetition are connected through two pathways, one running dorsally and the other ventrally. Diffusion tensor imaging (DTI) studies suggested that the fronto-temporo-parietal pathway (e.g., dorsal pathway) mainly encompasses the AF. Although this pathway was classically thought to connect Broca's and Wernicke's areas (Geschwind, 1970), modern tractography techniques have shown a more complex pattern of connectivity for this tract. As depicted in Figure 9, three principal branches have been identified as part of the AF: (1) long AF segment; (2) anterior AF segment; and (3) posterior AF segment. The long segment (direct pathway) directly connects Broca's and Wernicke's areas, corresponding with the classically described AF (Geschwind, 1970). The other two segments conform an indirect route, with the anterior segment connecting Broca's area with the IPC (Geschwind's territory), and the posterior segment linking the IPC and Wernicke's area. Previous studies using DTI-tractography have found different patterns of lateralization for the segments of the AF. Thus, the long segment is normally strongly left lateralized, the anterior segment is right lateralized, and the posterior segment has a bilateral distribution (Catani et al. 2007; Lopez-Barroso et al. 2013; Thiebaut de Schotten et al. 2011). However, individual and sex differences exist (Thiebaut de Schotten et al., 2011) (see further discussion in a next section). Although not completely related to language functions, the superior longitudinal fasciculus (SLF), a fronto-parietal tract, is often confused with the AF. Three components (i.e., I, II, III) have been identified for the SLF (Thiebaut de Schotten et al. 2011), with components I and II running dorsally to the AF, and component III corresponding with the anterior segment of the AF. This explains why in the literature the terms AF and SLF are often used interchangeably.

Moreover, the ventral pathway encompasses different white matter bundles connecting frontal and temporal areas including the IFOF, ILF and UF. All these tracts converge at the anterior extreme capsule (EmC), crossing from the temporal to the frontal lobe, as has been shown in studies involving monkeys (Schmahmann et al., 2007) and humans (Anwander, Tittgemeyer, von Cramon, Friederici, & Knösche, 2007). The IFOF, or also called extreme capsule fiber system (ECFS) (Friederici & Gierhan, 2013), connects the medial and lateral orbitofrontal cortex (BA47) and the occipital cortex passing by STG and MTG. The ILF connects the occipital (lateral and ventrolateral parts) to the anterior temporal lobe with some branches reaching hippocampus and amygdala (Catani & Thiebaut de Schotten, 2008; Herbet, Zemmoura, & Duffau, 2018). Lastly, the UF connects the anterior part of the IFG (pars orbitalis) and frontal operculum with the anterior temporal lobe

(Friederici & Gierhan, 2013). Generally, ventral pathways show similar volume in the right and left hemisphere. The pathways that conform the dorsal and ventral pathways are illustrated in Figure 9.



**Figure 9.** White matter tracts involved in verbal repetition.

## 6.2. Evidence from persons with aphasia: lesion-based approaches

Certainly, a great amount of the knowledge on the neural basis of verbal repetition comes from studies of patients with brain damage. Complementing the previously exposed evidence, lesion approach studies have focused on identifying brain structures that are crucial for verbal repetition and, thus, on identifying the lesions that are likely to cause aphasias with repetition impairments (e.g., CA). In this regard, considerable efforts have been made to disentangle the role of two structures that were suggested by independent studies to be crucial for repetition: (1) the AF, the main white matter bundle of the dorsal stream, and (2) the Sylvian–parietal–temporal area (Spt).

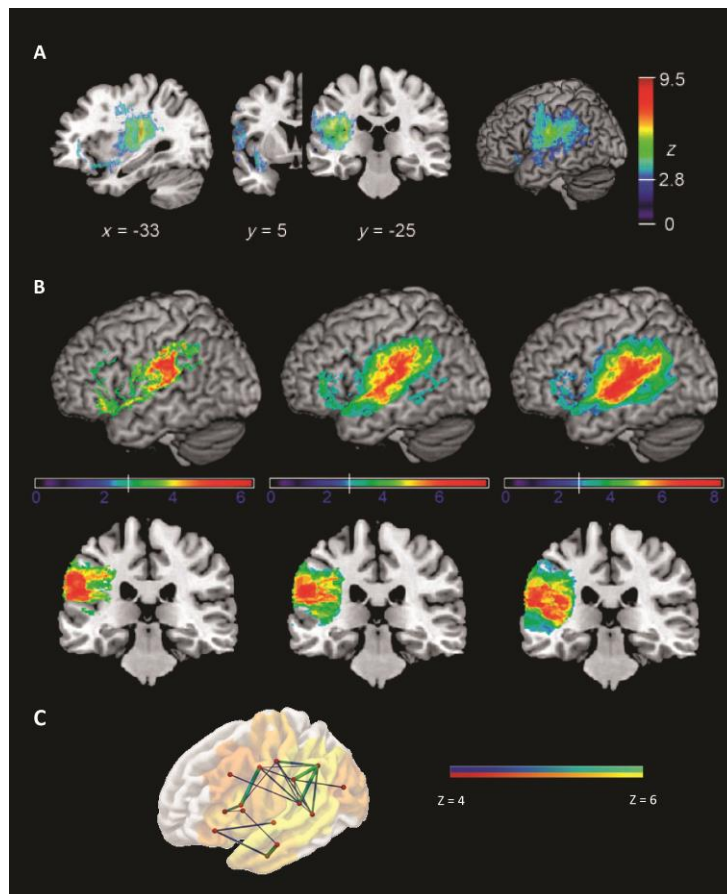
Several studies have delineated a link between damage to the AF and repetition deficits in brain-damaged individual as observed, for instance, in CA. In fact, Geschwind was the first author proposing that lesions to this bundle will result in CA as a consequence of the disconnection between frontal and posterior areas (Catani & Mesulam, 2008; Geschwind, 1974). This early idea was further supported by modern lesion-approach analyses. For instance, DTI-based studies of PWA showed that lesions in the AF correlated with the severity of repetition impairment (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Kümmerer et al., 2013, but see Bernal & Ardila, 2009). In this line, some studies have shown that in most cases, persons presenting with CA have affection of the AF (Jones et al., 2014; Zhang et al., 2010). However, a different position argues that repetition deficits are better

explained by cortical dysfunction than by white matter damage (Hickok & Poeppel, 2004). In this sense, some studies have suggested that since the area Spt responds to both speech perception and production (Buchsbaum et al., 2001; Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Hickok, Okada, & Serences, 2009), it represents an auditory-motor interface crucial for verbal repetition. In this line, some studies using VLSM analysis have evidenced that deficits in verbal repetition tasks are associated with damage to Spt among others areas (Baldo et al., 2012; Rogalsky et al., 2015). Likely, lesion analyses of patients with CA have shown that areas of maximum lesion overlap encompassed Spt (Buchsbaum et al., 2011). Yet, the results of these studies cannot explain cases of CA with selective involvement of the AF (see discussion in Berthier et al., 2012) nor the CA cases with sparing of the left Spt (Jones et al., 2014).

The claim in favor of cortical involvement as critical element of repetition deficits is further supported by cases of preserved repetition despite AF involvement (Shuren et al., 1995), and impaired repetition without AF involvement (Anderson et al., 1999). However, it can be argued that at least three factors may explain that variability. The first is that some negative cases (Shuren et al., 1995; Anderson et al., 1999) had long-lasting epilepsy which may have induced brain reorganization. Second, the negative evidence may have coincided with the moment of spontaneous recovery occurring during the first months after brain damage, meaning that a lesion to the AF may cause repetition deficits early after brain damage but be hastily reversed due to compensatory mechanisms. For instance, rapid recovery of repetition was described in three cases of CA after selective lesion to the AF (Tanabe et al., 1987). Linked to the previous one, the third factor is related to anatomical differences in the development of the right AF (Berthier et al., 2012), which has been suggested to show individual differences in the lateralization pattern, being left lateralized in some cases and bilaterally distributed in others (Catani et al., 2007). This come to say that greater development of the right segment may aid recovery of repetition deficits. In fact, this latest factor was suggested to explain contrasting repetition abilities (i.e., preserved vs impaired) in PWA showing similar lesion location and volume (Berthier et al., 2013).

Given that these structures work in concert to achieve normal performance, and that both the AF and Spt area are closely located, it is probable that a lesion encompassing the tempo-parietal region will affect both structures. Thus, the reasonable position is to suggest that lesions affecting both the AF and the Spt contribute to repetition impairments. Actually, this is fully supported by recent lesion-behavior mapping (e.g., VLSM) studies, which suggest that an extended network is involved in verbal repetition, encompassing the left posterior STG, MTG, left SMG, and the adjacent white matter (Fridriksson et al., 2018;

Henseler et al., 2014; Kümmerer et al., 2013; Pilkington et al., 2017; Ripamonti et al., 2018) as well as articulatory-related areas such as PMC, IC and IFG (Fridriksson et al., 2018; Kümmerer et al., 2013; Ripamonti et al., 2018) —(Figure 10, panel A and B). Thus, lesion-network approaches suggest that repetition deficits are predicted by damage to an extensive cortical network involving dorsal and ventral areas (Fridriksson et al., 2018) —(Figure 10, panel C). Interestingly, increasing the complexity of the to-be repeated material gradually increases the extension of cortical areas crucial for performing the task (Henseler et al., 2014) —(Figure 10, panel B).



**Figure 10.** Lesioned voxels depicting high negative correlations with repetition performance. **(A)** Voxelwise lesion-behavior map for repetition scores. Color bars indicate z-scores at  $p < .01$ , FDR corrected. Numbers indicate coordinates in MNI space. Figure and legend adapted from Kümmerer et al. (2013). **(B)** VLSM-maps showing significant voxels associated with the impaired repetition of phonemes (left), 1-syllabic words (middle) and sentences (right). All voxels shown exceeded the critical threshold for significance (indicated by the white line in the colour bars,  $p < .05$  FDR-corrected). Lighter colors reflect increasing Z-scores. Figure and figure legend adapted from Henseler et al., 2014. **(C)** Results from Univariate Region-wise lesion-symptom mapping (RLSM; red-yellow) and Connectome lesion-symptom mapping (CLSM; blue-green), two lesion-behavior like analyses that, in this case, indicate how strongly damage to a given region and connection (respectively) predicts scores in a repetition task. Figure and figure legend adapted from Fridriksson et al. (2018).

Importantly, plastic changes and preexisting differences within the repetition networks, and right homologues components, may influence the degree of recovery in PWA and the emergence of extraordinary language abilities in models of language expertise. Given that these aspects are of concern for the purpose of this dissertation, in the next section I will review plastic changes occurring in non-damage brains when mastering an ability relying on the auditory-motor network, the mechanisms supporting language improvements after brain damage and the role that pre-existing individual differences, particularly sex, may have in this processes.

## **7. Mechanisms underlying language expertise and recovery after brain damage**

### **7.1. General mechanisms supporting expertise in auditory-motor processes**

Advantages in auditory-motor abilities are associated to improved linguistic and musical performance. Several studies have addressed functional and anatomical brain differences related to linguistic and musical training showing that expertise in these domains is accompanied by long-lasting differences in cortical areas and tracts encompassing the bilateral dorsal and ventral streams, motor-related and domain-general processes areas. Yet, the direction of these differences is variable across studies, and sometimes complex to interpret.

Short periods of musical and linguistic training are generally associated with increased grey matter volume, increased activity and lower diffusion (e.g., greater fractional anisotropy [FA] or lower radial diffusivity [RD]) in relevant components (e.g., auditory-motor network) (Imfeld, Oechslin, Meyer, Loenneker, & Jancke, 2009; Lahav, Saltzman, & Schlaug, 2007; Mårtensson et al., 2012). Yet, early acquisition of audio-motor skills and prolonged training seem to induce a more complex reshaping of brain structure and functioning. In this regard, both increased (Golestani, Price, & Scott, 2011) and decreased (Elmer et al., 2014) grey matter volume were reported associated to linguistic expertise (e.g., phoneticians or simultaneous interpreters). To cite an example, Golestani and colleagues (2011) reported that years of training in phonetic transcription positively correlated with IFG volume. Moreover, musical training was shown by some studies to elicit a complex pattern with increase gray matter volume in some areas but decrease in others (James et al., 2014; Vaquero et al., 2016). However, other studies only reported greater volume in musician compared to non-musician (Gaser, Schlaug, & Scott, 2011; Han et al., 2009) (for a review of studies of neuroplasticity in musicians see table 1 in Vaquero et al., 2016). In the same line, tractography-based

analyses have evidenced white matter microstructural changes associated to language and musical expertise. For instance, studies of phoneticians (Golestani et al., 2011; Vandermosten et al., 2016) and simultaneous interpreters (Elmer, Hänggi, Meyer, & Jäncke, 2011) reported reduced FA in tracts associated to auditory-motor processing, such as the long segment of the AF (Vandermosten et al., 2016), while another study of simultaneous interpreters reported a much complex pattern of white matter microstructure with greater FA in some tracts and lower in others (Elmer et al., 2019). Similarly, early musical training was associated with increased FA as reported by some studies, and with decreased FA (Schmithorst & Wilke, 2002) and increased mean diffusivity (MD) as reported by others (Imfeld et al., 2009).

Discrepancies in the direction of brain changes associated to auditory-motor expertise are difficult to explain in the light of the current knowledge, since results cannot be interpreted in a straightforward manner. Reduced grey matter volume in relevant cortical areas is often found in degenerative diseases (Busatto et al., 2003; Wang et al., 2015) and associated to lower performance in, for instance, language tasks (Amici et al., 2007), but lower volume not always correlates with lower performance. Actually, decreased volume in frontal areas due to synaptic pruning is a hallmark of brain maturation (Giorgio et al., 2010; Sowell, Thompson, Tessner, & Toga, 2001). Certainly, lower FA and/or greater radial (RD) and MD are normally linked to pathological states, due to the association of these parameters with decrease myelination and lower axonal packing (Alexander, Lee, Lazar, & Field, 2007; Neil, Miller, Mukherjee, & Hüppi, 2002). Yet, this is likely to be an oversimplification, as anisotropy is influenced by many other factors (e.g., amount of crossing fibers, axon diameter and so on), with axonal membrane properties having a main role (Beaulieu, 2002, 2009; Neil et al., 2002). Therefore, while in pathological cases neuroimaging results are interpreted in a straightforward direction (greater diffusivity and reduced grey matter volume correlate with dysfunctional states), this does not seem to always apply for cases of prolonged training and early acquired abilities in non-pathological studies.

Regarding expertise, an important issue is that in many cases is difficult to establish whether the observed brain differences are induced by training, are pre-existent or are the result of an interaction of both factors (Wan & Schlaug, 2010). Strong evidence in favor of training-induced differences comes from studies showing correlation between amount of training and structural or functional differences (Golestani et al., 2011; Halwani, Loui, Rüber, & Schlaug, 2011). Conversely, evidence that pre-existent differences may favor performance comes from studies showing that individual differences in the auditory-motor network predicts imitation abilities, as well as music and language learning (Assaneo et al., 2019;



Lopez-Barroso et al., 2013; López-Barroso et al., 2011; Lucía Vaquero, Ramos-Escobar, François, Penhune, & Rodríguez-Fornells, 2018; Lucía Vaquero, Rodríguez-Fornells, & Reiterer, 2016).

Importantly, the study of expert models provides a deeper understanding of the brain signatures that enable outstanding performance in auditory motor abilities, informing models of neuroplasticity. Also, understanding the brain changes occurring when one master a linguistic function may enlighten the development of therapeutic approaches for PWA, by pointing out putative brain components that may be enhanced to aid performance. In the next section, I review the neural reconfiguration mechanisms underlying the recovery from aphasia.

## **7.2. General mechanisms and structures supporting language recovery in aphasia**

Spontaneous recovery of functions after brain damage is frequent during the first months. Importantly, these spontaneous changes may be potentiated by therapy afterward during the chronic stage. Yet, while the mechanisms responsible for rapid recovery may be related to restored blood flow or hematoma reduction (Berthier et al., 2011; Hillis et al., 2006), recovery beyond the acute phase is likely to be driven by neural reconfiguration across preserved brain networks and within the preserved areas of the damaged network/s. Different hypotheses have been postulated regarding brain changes associated with language recovery after brain damage. These hypotheses refer to: (1) the recruitment of perilesional dysfunctional but still viable neural tissue and the unmasking of function of non-affected nodes in the left hemisphere; (2) the compensatory involvement of homologues areas on the right hemisphere; and (3) the combination of (1) and (2), which acting together support language improvement (Berthier et al., 2011; Schlaug, 2018; Turkeltaub et al., 2011).

Longitudinal studies have suggested that the contribution of spared areas of the left hemisphere and undamaged areas of the right hemisphere to language recovery change over time (Hartwigsen & Saur, 2017). As a general pattern, greater involvement of ipsilateral areas in the acute phase are expected, then compensation via right networks at later stages (sub-acute/chronic) may take place, to finally shift back to the left hemisphere in the chronic stage (Hartwigsen & Saur, 2017; Saur et al., 2006). However, there is great variability in the recovery pattern of PWA, and this issue has not received enough attention. It has been posited that at individual level many variables may influence which networks are recruited during recovery and the degree of recovery reached. Amongst other important factors, the features related to the lesion (i.e., lesion location and lesion size), initial aphasia type and severity,

and type of treatment received (Watila & Balarabe, 2015) stand out. Regarding lesion-related factors, available evidence suggests that the recruitment of the right hemisphere depends, in fact, on the extension and location of the damage in language-related regions of the left hemisphere (Anglade, Thiel, & Ansaldo, 2014). For instance, it has been shown that PWA and lesions compromising the left IFG show both recruitment of perilesional areas such as anterior IC and homologous nodes of the right hemisphere (Turkeltaub et al., 2011), while patients with preserved left IFG only recruit perilesional areas. Further, several studies have pointed out that lesion load of the left AF—meaning the proportion of the tract affected—and the development of the right AF are powerful predictors of aphasia recovery (Forkel et al., 2014; Geva, Correia, & Warburton, 2015; Hillis et al., 2018; Jehna et al., 2017; Marchina et al., 2011).

Improvements restricted to some linguistic abilities may depend on the strengthening of specific components of the residual and contralateral language networks, which may selectively be modulated by the nature of the therapy. For instance, our research team demonstrated that modulation of brain plasticity with a combined therapy (a drug modulating the cholinergic system and intensive imitation-repetition therapy), significantly improved verbal communication in a PWA by inducing structural plasticity of the frontal aslant tract (FAT) of the damaged hemisphere (Berthier et al., 2017), a key white matter pathway involved in verbal fluency (Catani et al., 2013). Furthermore, a reduction of semantic errors induced by intensive language therapy was associated to structural plasticity within the left ventral stream (McKinnon et al., 2017). In the same vein, improvements in speech production induced by MIT have been associated with structural changes in the right AF (Schlaug et al., 2009). Moreover, since stroke induces networks alterations, enhancement of functions may be accompanied by large scale reconfiguration, for example by increasing temporal synchronization among language-relevant and compensatory areas, or increasing modularity (Klingbeil et al., 2019). For instance, improvements in the number of correct syllables in a repetition task induced by combined language therapy and non-invasive brain stimulation, correlated with increased resting state functional connectivity among several nodes of the left hemisphere (Marangolo et al., 2016) (for a review see Klingbeil et al., 2019).

### **7.3. Support between dorsal and ventral pathways to aid linguistic performance**

Evidence indicates that although the dorsal and ventral streams are anatomically and functionally segregated, a synergistic cooperation between them is possible (Makris & Pandya, 2009; Rauschecker & Scott, 2009; Rolheiser, Stamatakis, & Tyler, 2011; Weiller,

Bormann, Saur, Musso, & Rijntjes, 2011). Nevertheless, the type and sites of interaction between these two language streams is still elusive. In this regard, Cloutman (2013) proposed three models of interaction between the two streams. The first account considers that although both streams process information independently, the transferred information along the pathways is integrated at a final destination in the cerebral cortex. The second hypothesis maintains that separate information along the two pathways is modulated by feedback loops within one such stream and also between streams. Finally, the third account suggests the existence of a crosstalk between the two streams at multiple stages and sites. These standpoint theories open a number of perspectives for future research.

One important question is if under certain circumstances (e.g., brain damage), the functions of one stream can be compensated, or further supported, by the other and if this compensation is adaptive (if it improves language deficits, or not). In the same line, it also remains unclear whether further recruitment of an additional stream, even in normal circumstances, may support the improvement of functions, and therefore, support extraordinary verbal abilities. To cite just an example, previous neuroimaging studies with healthy population revealed that although in normal circumstances the left dorsal stream is in charge of verbal repetition processes required to learn auditory-presented new words (López-Barroso, Catani, Ripollés, Dell'Acqua, Rodríguez-Fornells, & de Diego-Balaguer, 2013; López-Barroso, Ripollés, Marco-Pallarés, Mohammadi, Münte, Bachoud-Lévi, et al., 2015), the left ventral stream may take over these duties when the ipsilateral dorsal stream is artificially blocked in healthy subjects (López-Barroso, de Diego-Balaguer, Cunillera, Camara, Münte, Rodríguez-Fornells, 2011).

The compensatory potential of language-related streams on the right and left hemisphere are further addressed in the main corpus of the present dissertation (i.e., *Study 1, Study 3, Study 4 and 5*). In next section I analyze individual and sexual differences as putative sources of variability in phonological processing abilities.

#### **7.4. Sources of variability in verbal repetition abilities**

The concept of *degeneracy* stands out as a mechanism explaining differences in language outcome after brain damage and different brain-behavior relationship across individuals. This has been defined as “the ability of elements that are structurally different to perform the same function or yield the same output” (Edelman & Gally, 2001) and it was used to describe the situation in which more than one structure (or system) support a given function or task, being each of these sufficient (Friston & Price, 2003; Noppeney, Friston, & Price, 2004). *Degeneracy* within subjects (Price & Friston, 2002) was proposed as a

mechanism supporting: (1) cognitive functions resilience after damage; and (2) recovery of functions after brain damage, as multiple systems may support the same function. By this, language deficits and recovery of functions after brain damage will be influenced by individual differences, for instance premorbid language lateralization and structural and functional differences. Likely, *degeneracy* across subjects has been proposed as a mechanism to explain neurofunctional inter-individual differences, since the same task may be supported by different neural networks across individuals. In other words, equal performance in a given task may be supported by different neural mechanisms across subjects reflecting the implementation of different cognitive strategies (Noppeney et al., 2004). This stands as an important concept to understand different language outcomes after brain damage (e.g., aphasia) in light of similar lesions, as well as to explain individual differences in neural systems supporting expertise, which are of relevance in *Study 4* and *Study 5* of the present thesis.

A potential source of individual differences in brain structure and functioning is sex. Sex differences in the human brain have been recognized for more than one century (Woolley 1910). A variety of neuroimaging studies on sex differences examining structure, patterns of brain activation and connectivity have suggested that the configuration of language-related networks vary among females and males (Catani et al., 2007; Ruigrok et al., 2014; Thiebaut de Schotten et al., 2011). Given that anatomical differences seem to play an important role in the clinical expression and recovery after brain damage (Berthier et al., 2013; Forkel et al., 2014), it will be important to determine whether sex differences exist in the prevalence of some aphasic syndromes. This issue is addressed in *Study 5*, where the proportion of females and males in aphasias characterized by preserved and impaired repetition is estimated based on a literature review of published cases of CAs and TAs.

# CHAPTER 2



## Chapter 2. Research aims

As presented in the *Introduction* section, the neural network involved in repetition has been extensively studied. Findings evidenced that this ability is supported by a distributed neural network encompassing sensory and motor areas. Yet, clinical issues regarding pathological verbal repetition have not been addressed within the light of modern neuroscience, and behavioral and neural individual differences had been overlooked.

The crosscutting aim of the present dissertation is to explore the clinical, cognitive and neural features of verbal repetition, moving from a dysfunctional ability to expertise level. The present thesis comprises five studies that are organized into two blocks. *Block 1* encompasses three studies focused on altered verbal repetition behaviors in PWA, in an attempt to provide fresh information on the compensatory plastic mechanisms underlying them. *Block 2* comprises two studies that aim to explore sources of individual differences in repetition abilities, including verbal expertise and verbal repetition after brain damage. Next, I state the specific goal pursued in each study.

### *Block 1:*

- **Study 1** aims to examine neural and cognitive features of mitigated echolalia and *conduite d'approche*—two frequent but unexplored repetitive verbal behaviors in aphasia—in three persons with chronic post-stroke aphasia. Specifically, this study explores if these symptoms emerge as a consequence of the overreliance on one route (e.g., dorsal) when the other one (e.g., ventral) is affected. For this purpose, multimodal evaluation including language and cognitive assessments as well as different neuroimaging techniques are used.
- **Study 2** has the objective of reviewing the symptom of echolalia (which refers to the repetition of words and utterances spoken by another person) in the context of aphasia. Specifically, it aims to provide a reappraisal of the characteristics of the different types of echolalia, exploring its possible causes, and providing directions for its clinical assessment and treatment.
- **Study 3** aims to further explore the most frequent subtype of echolalia (mitigated echolalia) in a person with fluent aphasia and impaired auditory comprehension. For this, the symptom of ME is analyzed at behavioral and brain levels while trying to elucidate its different purposes in different linguistic contexts. Since in this case ME interfered with functional communication, a second objective was to study the efficacy of a combined treatment (i.e., memantine and intensive language-action therapy) in reducing instances of echolalia.

*Block 2:*

- **Study 4** aims to characterize the common features and the individual differences at cognitive and brain levels of two healthy subjects with an extraordinary ability to reverse language as assessed through forward and backward repetition tasks. At large, built on a multidimensional approach, this study sought to offer insights on the cognitive strategies and the structural and functional neural distinctiveness that characterize outstanding performance in auditory-motor based linguistic task.
- **Study 5** explores sex-related differences in the ability of verbal repetition after brain damage. Specifically, the aim of this study is to analyze sex-distribution in two types of aphasias, one characterized by impaired verbal repetition abilities (i.e., CA) and the other by preserved repetition (i.e.,TA). This will provide evidence on whether sex differences in the frequency of verbal repetition deficits exist in among PWA. The hypothesis of this study was based on the previous exposed evidence suggesting sex brain-dysmorphisms in language-related areas.



# CHAPTER 3



## **Chapter 3. Main corpus**

### **Block 1: Pathological repetition: neural features and the clinical approach**



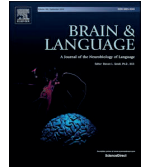
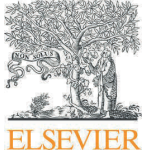
***Study 1. Repetitive verbal behaviors are not always harmful signs: Compensatory plasticity within the language network in aphasia<sup>1</sup>***

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<sup>1</sup> This study corresponds to:

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## Repetitive verbal behaviors are not always harmful signs: Compensatory plasticity within the language network in aphasia



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### A B S T R A C T

Repetitive verbal behaviors such as *conduite d'approche* (CdA) and mitigated echolalia (ME) are well-known phenomena since early descriptions of aphasia. Nevertheless, there is no substantial fresh knowledge on their clinical features, neural correlates and treatment interventions. In the present study we take advantage of three index cases of chronic fluent aphasia showing CdA, ME or both symptoms to dissect their clinical and neural signatures. Using multimodal neuroimaging (structural magnetic resonance imaging and [18]-fluorodeoxyglucose positron emission tomography during resting state), we found that despite of the heterogeneous lesions in terms of etiology (stroke, traumatic brain injury), volume and location, CdA was present when the lesion affected in greater extent the left dorsal language pathway, while ME resulted from preferential damage to the left ventral stream. The coexistence of CdA and ME was associated with involvement of areas overlapping with the structural lesions and metabolic derangements described in the subjects who showed one of these symptoms (CdA or ME). These findings suggest that CdA and ME represent the clinical expression of plastic changes that occur within the spared language network and its interconnected areas in order to compensate for the linguistic functions that previously relied on the activity of the damaged pathway. We discuss the results in the light of this idea and consider alternative undamaged neural networks that may support CdA and ME.

### 1. Introduction

Traditional descriptions of aphasia have ascribed language disturbances to tissue damage involving different cortical areas, deep grey nuclei and their associative white matter connections (Albert, Goodglass, Helm, Rubens, & Alexander, 1981; Damasio & Damasio, 1992). This brain-language relationship seems to be suitable to account for the loss or impoverishment of previous language abilities (e.g., reduced auditory comprehension, word finding difficulty, faulty repetition), hereafter referred to as “residual language deficits”. However, it is evident that, despite having lost some language abilities, persons with aphasia (PWA) indefatigably attempt to communicate and this often leads to the emergence of either correct verbal emissions or speech errors, sometimes in the form of repetitive verbal behaviors (RVBs) (recurrent utterances, paraphasias, perseverations and echolalia) (Wallesch, 1990). The neural correlates of correct verbal emissions and

RVBs seem to be different from the ones subserving residual language deficits, since the former cannot emanate from a fully dysfunctional network affected by irreversible tissue damage or absent blood flow and metabolic activity. Following this line of reasoning, RVBs cannot be explained by the direct effect of the lesion. Rather, their occurrence may reflect neural changes attempting to compensate the residual language deficits via recruitment of undamaged brain networks (Fridriksson, Baker, & Moser, 2009). These plastic changes may occur spontaneously or promoted by aphasia therapy even well beyond the acute stage (Hartwigsen & Saur, 2017).

Using a lesion-deficit approach, recent efforts have been directed to examine the relationship between tissue damage and residual language deficits through neuroimaging methods such as voxel-based lesion-symptom mapping (Bates et al., 2003; Dell, Schwartz, Nozari, Faseyitan, & Branch Coslett, 2013; Mirman et al., 2015; Schwartz et al., 2009), voxel-based correlational methodology (Halai, Woollams, &

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*Study 2. Thinking on treating echolalia in aphasia: Recommendations and caveats for future research directions<sup>2</sup>*

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# Thinking on Treating Echolalia in Aphasia: Recommendations and Caveats for Future Research Directions

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**Keywords:** imitation, repetition, echolalia, aphasia therapy, memantine

## ARE VERBAL IMITATION AND REPETITION THE SAME?

Imitation in the form of repeating speech sounds, accents, and words plays a foundational role in the normal acquisition and development of language (Meltzoff et al., 2009; Adank et al., 2013) eventually contributing to a life-long fine-tuning of communication skills (Tannen, 1987; Delvaux and Soquet, 2007). Imitation of prosodic and paralinguistic features may be intentional in certain contexts (e.g., mockery, impersonation, acting rehearsal). However, in general, imitation in healthy subjects is unintended as it involves automatic mimicry of non-essential components of the acoustic-phonetic information (speaking rate, prosody, accent) embedded in the heard message (Kappes et al., 2010)—the so-called *chameleon* effect. Therefore, it seems that verbal imitation is not the same as verbal repetition because in the latter, the auditory stimulus is intentionally repeated and the reproduced speech contains relevant phonological information, but the incidental acoustic features of the perceived stimulus are not invariably mimicked (Kappes et al., 2009, 2010).

## ECHOLALIC REPETITION AND ITS SUBTYPES

Echolalia, the repetition of words and/or utterances spoken by another person (Wallesch, 1990), is frequently documented in individuals with autism spectrum disorders (Stiegler, 2015), neurodegenerative dementias (Da Cruz, 2010; Kertesz et al., 2010), post-stroke aphasia (Geschwind et al., 1968; Christman et al., 2004), and other neurologic and psychiatric disorders (Berthier et al., 2017a). However, there are no studies on the prevalence of echolalia in these conditions. This is intriguing as, for instance, echolalia is a usual accompanying feature of transcortical aphasias, which represent 4–20% of all aphasias (Berthier, 1999). Moreover, echolalia has occasionally been described during the recovery process of classical perisylvian aphasias (global, Wernicke, conduction, Broca; Brown, 1975; Hadano et al., 1998; López-Barroso et al., 2017). This implies that a more in depth assessment would inflate the prevalence rates.

Echolalia is a heterogeneous symptom of aphasia and several subtypes have been described (Wallesch, 1990; Berthier, 1999). More than one type of echolalia can coexist in the same patient (Brown, 1975; Hadano et al., 1998) and changes from one form to another (i.e., from *complete* to *partial*) during aphasia evolution is common. The most severe types of echolalia occur in aphasias with preserved repetition abilities (transcortical aphasias; Berthier et al., 2017a). Two of them,

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***Study 3. Are you a doctor? ... Are you a doctor?  
I'm not a doctor! A reappraisal of mitigated  
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## Are you a doctor? ... Are you a doctor? I'm not a doctor! A reappraisal of mitigated echolalia in aphasia with evaluation of neural correlates and treatment approaches

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### ABSTRACT

**Background:** Mitigated echolalia (ME) is a symptom of aphasia which refers to a seemingly deliberate repetition of just-heard words and phrase fragments. ME has historically been viewed as a compensatory strategy aimed to strengthen auditory comprehension. Nevertheless, this hypothesis and other possible functional deficits underlying ME have not been evaluated so far.

**Aims:** This study aimed to (a) reappraise ME in the frame of modern neuroscience; (b) report the effects of Constraint-Induced Aphasia Therapy (CIAT) and a cognition-enhancing drug (memantine) on detrimental ME in a patient (CCR) with fluent aphasia; and (c) analyse the functional and structural brain correlates of ME in CCR with multimodal neuroimaging.

**Methods & Procedure:** Tasks tapping verbal expression and auditory comprehension were administered to CCR to evaluate ME. After baseline testing, evaluations were performed under placebo alone (weeks 0–16), combined placebo with CIAT (weeks 16–18), placebo treatment alone (weeks 18–20), washout (weeks 20–24) and memantine (weeks 24–48). Instructions to reduce ME during CIAT were provided to CCR. Language evaluation and multimodal neuroimaging were also performed 10 years after ending treatment.


**Outcomes & Results:** At baseline, ME occurred in spontaneous speech and in difficult-to-understand single words, indicating impaired meaning access. However, more instances of ME were heard in sentence comprehension, reflecting additional impairment in short-term memory. ME also occurred in words that were correctly defined and understood to the extent that even after accessing word meaning successfully, CCR repeated the same word several times, suggesting impaired inhibitory response control. In comparison with baseline, analysis of auditory sentence comprehension under treatment revealed significant decrements of ME just after ending CIAT and 2 weeks later. These gains were


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## **Block 2: Individual/sex differences in verbal repetition and phonological processing**



## *Study 4. Language in reverse: Behavioral and neural correlates of backward repetition<sup>4</sup>*

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## **Language in reverse: Neurocognitive correlates of expert phonological encoding in backward speakers**

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## Abstract

Despite its prolific growth, neurolinguistic research on phonological encoding has largely neglected the study of phonemic sequencing mechanisms –namely, the neurocognitive systems supporting the linear organization of phonemes. To bridge this gap, the present study reports multidimensional signatures of two experts in backward speech, that is, the capacity to produce utterances by reversing the order of phonemes while retaining their identity. Our approach included behavioral assessments of backward and forward speech alongside measures of voxel-based morphometry, diffusion tensor imaging, and resting-state functional connectivity. Relative to controls, both backward speakers exhibited behavioral advantages for reversing words and sentences of varying complexity, irrespective of working memory skills. These patterns were accompanied by increased grey matter volume, increased mean diffusivity, and enhanced functional connectivity along dorsal and ventral stream regions mediating phonological and otherwise linguistic operations, with complementary support of areas mediating associative-visual and domain-general processes. Still, the specific loci of these neural patterns differed between both subjects, suggesting individual variability in the correlates of expert backward speech. Taken together, our results offer new vistas on the relatively underexplored domain of phonological sequencing, while illuminating neuroplastic patterns underlying expert language processing.

**Keywords:** backward speech, phonemic sequencing, voxel-based morphometry, diffusion tensor imaging, functional connectivity.



## Introduction

When visiting the local barber shop, a native Spanish speaker from La Laguna, Spain, may be caught off guard by the parlance of some compatriots. He might be greeted with the utterance *nasbue chesno* and fail to understand it at all. With time, however, he may realize that the phrase was a backward rendition of *buenas noches* (*good evening*) and that this peculiar way of speaking is quite widespread in this town. So much so, in fact, that a group of citizens demand that UNESCO acknowledge their linguistic extravaganza as intangible cultural heritage. Still, theirs might be a lost cause. Although word inversion is also part of other sociolects, such as Argentine *lunfardo*, the Canary Academy of Language has declared that this phenomenon has no scholarly value.

Yet, that position is arguably short-sighted. Backward speech constitutes an extraordinary ability to quickly reverse words, pseudowords, and even sentences, which requires reordering phonemes while retaining their identity. Therefore, it offers a useful model to study phoneme sequencing –i.e., the capacity to select, retrieve, and temporarily arrange sounds needed to set up an articulatory plan (Dell, Burger, & Svec, 1997; Hartsuiker et al., 2005; Levelt, Roelofs, & Meyer, 1999). In this sense, whereas various aspects of phonological-phonetic encoding have been studied in patient samples (Han et al., 2016; Laganaro, Python, & Toepel, 2013; Laganaro & Zimmermann, 2010; Wilshire, 2002), the neurocognitive mechanisms underlying phoneme sequencing skills remain notoriously overlooked in models of language expertise. To bridge this gap, here we combined behavioral assessments with structural and functional brain imaging methods to examine multidimensional signatures of backward speech in two healthy expert backward talkers.

Backward speech can manifest in different forms depending on the reversed unit. At word level, reversal may be done by rearranging phonemes (e.g., *basket* becomes *teksab*) or syllables (e.g., *basket* becomes *ketbas*) (Cowan, Braine, & Leavitt, 1985). At sentence level, the above operations may be performed while the constituents are also reversed (i.e., starting from the last word and going backwards to the first one, such that *basket is fun* becomes *nuf si teksab*) or while their syntactic ordering is preserved within the phrase (e.g., *basket is fun* becomes *teksab si nuf*) (Cowan et al., 1985). Both forms of backward speech may be supported by inner visualization of written words or phrases (Coltheart & Glick, 1974; Cowan et al., 1985; Cowan & Leavitt, 1982; Jokel & Conn, 1999) or heightened working memory abilities (Cowan & Leavitt, 1982; Prekovic et al., 2016). Of note, backward speech proves particularly feasible in languages with transparent or relatively transparent orthography, such

as Spanish (Seymour, Aro, & Erskine, 2003), as this allows for phonemes to nearly always retain their identity (same sound) irrespective of their position and surrounding segments.

Although a number of studies have examined linguistic aspects of backward speech in healthy subjects (Chia & Kinsbourne, 1987; Coltheart & Glick, 1974; Cowan, Braine, & Leavitt, 1985; Cowan, Leavitt, Massaro, & Kent, 1982; Cowan & Leavitt, 1982, 1987), evidence on its neural signatures proves scant. The few case studies on pathological backward speech (Cocchi, Pola, Sellerini, Tosaca, & Zerbi, 1985; Jokel & Conn, 1999; Mitchell, 1903) provided but vague references to frontal or temporal lesions. More relevantly, the only study exploring *in vivo* neural correlates of this skill (in a healthy backward speaker with exceptional working memory abilities) showed greater activity during backward than during forward speech mainly in the bilateral inferior frontal gyrus (IFG), left superior temporal gyrus (STG), left supramarginal gyrus (SMG), and the left fusiform gyrus (FFG) (Prekovic et al., 2016). Of note, these areas are implicated in phonological processing and verbal working memory (Chein, Ravizza, & Fiez, 2003; Prekovic et al., 2016), with the FFG playing additional roles in visual imagery (Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002). This evidence suggests that backward speech (and with it, phonemic sequencing skills) would critically rely on dorsal stream regions, with less critical involvement of the ventral stream (Hickok & Poeppel, 2007; Saur et al., 2008). However, no study has systematically examined this issue, let alone integrating neuroanatomical and functional connectivity methods.

Following the dual-stream model of speech processing (Hickok & Poeppel, 2007; Saur et al., 2008), language processing critically relies on two segregated and interactive neural routes. Auditory-motor integration processes, including phonological encoding operations, would be mainly subserved by the dorsal stream, whereas lexico-semantic access and other functions would be critically supported by the ventral stream (Hickok & Poeppel, 2007; Saur et al., 2008). More particularly, core functions of the dorsal route (including verbal repetition and phonemic processes) are subserved by temporo-frontal areas directly connected through the long segment of the arcuate fasciculus (AF) (Catani, Jones, & Ffytche, 2005; Catani & Mesulam, 2008; Turken & Dronkers, 2011) and by two indirect segments: a parieto-temporal segment (posterior segment of the AF) and a parieto-frontal one (anterior segment of the AF) (Catani & Mesulam, 2008; Catani et al., 2005; Turken & Dronkers, 2011). On the other hand, the ventral stream comprises temporo-frontal areas connected through the inferior longitudinal fasciculus (ILF), the inferior fronto-occipital fasciculus (IFOF), and the uncinate fasciculus (UF) (Catani & Mesulam, 2008; Dick, Bernal, & Tremblay, 2014).

The more critical role of dorsal over ventral stream regions for phonemic sequencing is further supported by lesion-symptom analyses in aphasic patients. Indeed, the production

of phonemic paraphasias (misplacement of phonemes) and neologisms correlates with damage to dorsal regions (Stark et al., 2019), including the STG and SMG (Pilkington et al., 2017), the precentral and postcentral cortices (Schwartz, Faseyitan, Kim, & Coslett, 2012), and the underlying white matter (Han et al., 2016; Pilkington et al., 2017). Conversely, semantic paraphasias are more typically associated with ventral lesions, including the left middle and inferior temporal gyri (MTG, ITG) (Stark et al., 2019). However, this double dissociation is not always so clear cut. For instance, phonological processes also hinge on secondary contributions from the ventral stream, especially when dorsal regions are overloaded (Lopez-Barroso et al. 2011) or otherwise compromised (López-Barroso & Diego-Balaguer, 2017; Perani et al., 2011; Rauschecker et al., 2009; Torres-Prioris et al., 2019). Therefore, dorsal but also ventral stream brain regions emerge as potential putative sources of diverse phonological-phonetic encoding processes.

Against this background, we hypothesized that elevated phonemic sequencing skills, as exhibited by expert backward speakers, would be mainly associated with distinct brain signatures along the dorsal stream, with complementary markers in ventral stream areas. To test this conjecture, we profited from access to two expert backward speakers. First, we compared these subjects' language reversing abilities with those of non-expert controls, anticipating higher performance in tasks requiring phonemic inversion (i.e., backward speech) and assessing the influence of working memory abilities on the predicted effect. Second, relying on voxel-based morphometry (VBM) and diffusion tensor imaging (DTI), we tested the prediction that backward speakers would exhibit distinct structural configurations in dorsal stream regions and tracts (AF), with contributions of ventral stream areas and associated white matter tracts (ILF, IFOF, and UF). Third, we relied on functional connectivity analysis to explore whether dorsal and ventral stream regions also exhibited distinct patterns of resting-state coupling in both backward speakers. Briefly, building on this multidimensional approach, the present study seeks to offer novel insights on the neural underpinnings of phonological-phonetic encoding, in general, and phonological sequencing skills, in particular.

## **Methods**

### **Participants**

The study focused on two native Spanish speakers with an exceptional ability to reverse words and sentences, together with a sociodemographically matched control group. Backward speaker 1 (BS1) was a 43-year-old left-handed man with 17 years of formal education who worked as a system engineer. He had normal hearing and vision. Except for a

period of developmental stuttering between ages 10 and 12, he reported no history of other learning difficulties, psychiatric conditions or neurological disorders. BS1 realized that he could easily reverse words at age 14, in the absence of any explicit learning on this skill. Throughout his adulthood, he has constantly made deliberate (non-pathological) use of backward speech daily without resorting to any conscious strategy. For reversing words, he would rearrange each phoneme from last to first. For instance, he reversed the word *banana* as *ananab*. He stated that he typically reverses simple words effortlessly, whereas long words (e.g., *structuralism*) or long sentences prove more demanding. Notably, when faced with a sentence, he states that he can opt to reverse all words while keeping or reversing their original ordering. Yet, for the propose of assessment he was asked to employ the more frequently used form. Then, sentences reversal was done by keeping word's original order. None of BS1's relatives have ever presented this ability.

Backward speaker 2 (BS2) was a 50-year-old right-handed man with 14 years of formal education who worked as a photographer. His hearing and vision were normal, and he reported no history of learning difficulties or neuropsychiatric disorders. He effortlessly developed the ability to voluntarily reverse speech at age 8. Although he uses backward speech frequently, he has never explicitly practiced this skill. As in the case of BS1, his reversals operate on the phonemic (rather than the graphemic) level. His backward speech was also based on the words' phonological structure but, when reversing sentences, he only reversed them from the last to the first word. He reported that he cannot identify any specific, conscious strategy supporting his backward speech, although he declared being able to internally "see" flashes of the written words. The only family member with a similar skill was his 19-year-old daughter, although our behavioral assessment revealed that her performance was substantially poorer than BS2's (unpublished data).

The control sample for the behavioral study comprised 18 healthy men with a mean of 38.9 ( $SD = 10.9$ ) years of age and an average of 15.7 ( $SD = 1.8$ ) years of education. All subjects showed normal hearing and normal or corrected-to-normal vision, and reported no history of learning difficulties, psychiatric or neurological disorders, or drug or alcohol abuse. This sample was matched with both experimental subjects in terms of age (BS1: Crawford's  $t$ , two-tailed = .277;  $p = .785$ ; BS2: Crawford's  $t$ , two-tailed = .902;  $p = .379$ ) and education level (BS1: Crawford's  $t$ , two-tailed = .703;  $p = .491$ ; BS2: Crawford's  $t$ , two-tailed = - .919;  $p = .370$ ).

A different control group composed by 24 participants was used for the neuroimaging analyses, yet the number of participants included in each analysis varied (see section 2.4 below). All control participants were healthy men meeting the same inclusion and

exclusion criteria detailed above. These participants had a mean age of 32 years old ( $SD = 15.1$ ) and an average of 15 ( $SD = 3.1$ ) years of education. The whole sample was matched with both subjects for age (BS1: Crawford's  $t$ , two-tailed = .715;  $p = .482$ ; BS2: Crawford's  $t$ , two-tailed = 1.169;  $p = .254$ ) and education level (BS1: Crawford's  $t$ , two-tailed = .632;  $p = .533$ ; BS2: Crawford's  $t$ , two-tailed = -.316;  $p = .754$ ).

The study was approved by the Ethics Committee of the Institute of Cognitive Neurology (a host institution of the Institute of Cognitive and Translational Neuroscience). All participants provided written informed consent in accordance with the Declaration of Helsinki.

## **Behavioral assessment**

The behavioral assessments comprised two sets of tasks, aimed to test general cognitive skills as well as backward and forward language abilities. Testing was conducted in a quiet room over a single session lasting roughly 2 hours per subject. All evaluations were performed by the same examiner.

### **General cognitive tasks**

**Reasoning test:** Non-verbal reasoning was assessed through the Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 2002). In each trial, participants were presented through a PC screen with an incomplete array of shapes and had to point to one out of six possible pieces to complete the pattern. The test consists of 26 items, scoring 1 point for each correct answer and 0 for incorrect ones. Direct scores were transformed to a typified age-adjusted scale with a maximum possible score of 19.

**Forward and backward digit span:** These tasks were taken from WAIS-III (Wechsler, 2002). In the forward digit span task, subjects were required to repeat a sequence of numbers in the same order as the examiner. Stimuli were read aloud by the examiner. The number of digits presented ranged from two to nine, with two trials for each array, yielding a total of 16 trials. The maximum possible score was 16, with one point for each correct trial. For its part, the backward digit span task required subjects to repeat the sequence of digits in reverse order. The number of digits presented ranged from two to eight, with two trials for each number of digits (i.e., two sequences of two digits, two sequences of three digits, and so on), with a total of 14 trials. The maximum possible score was 14, with one point for each correct sequence. The task was interrupted if the subject could not complete any of the two trials with the same number of items. Given that typified age-adjusted scores are only available for the digit summed score (i.e., forward plus backward), direct scores were used.

**Operational span task:** This task (Unsworth, Heitz, Schrock, & Engle, 2005; Unsworth, Redick, Heitz, Broadway, & Engle, 2009) measures WM storage-plus-processing capacity using letters as to-be-remembered stimuli and math operations as the distractor task. Scores were calculated by summing the number of letters recorded correctly and in the right order (number of correct responses) and summing up the number of mistakes in math operations (speed and accuracy), named *math errors* (Unsworth et al. 2005). As in previous reports, only subjects with a performance of 85% or higher in the math operations entered the analysis (Unsworth et al. 2005) (for more details, see *Supplementary information*, section 1). This and next task were presented through E-prime 2.0 running on a Windows 7 PC.

**Symmetry span task:** The symmetry span task (Kane et al., 2004; Unsworth et al., 2009) was used to measure WM storage-plus-processing capacity when employing visuo-spatial information. This test resembles the operational span task but, in this case, participants were required to remember locations within a grid and judge whether a figure was symmetrical in its vertical axis or not as distractor. Two scores were calculated, namely: the number of correct positions and of symmetry errors. The former was obtained by summing up the number of locations remembered correctly and in the right presentation order; the latter was established by adding the number of accuracy and speed errors committed in the symmetry judgment trials. The criterion to determine speed errors was the same as that used for the operation span task but based on the time employed in the symmetry judgment trials (for more details, see *Supplementary information*, section 1).

### **Backward and forward language tasks**

Stimuli for the backward and forward language tasks were presented binaurally through Panasonic on-ear stereo headphones through an PC running with Windows 7. All stimuli were created via a computerized voice generator (text-to-word app included in Macintosh computers) and delivered through Psychtoolbox on Matlab software (v. 2016b) in .wav format, with a sampling rate of 44100 Hz. The volume of presentation was adjusted for each subject individually. In each task, the proportion of correct responses for each subject was calculated and compared to the mean proportion obtained by the control group.

**Forward and backward word and pseudoword repetition:** These two tasks were used to assess the subjects' capacity to repeat stimuli by sequencing their phonemes in the typical and reverse (i.e., backward) order. Importantly, in the latter case, instructions indicated that responses had to include all phonemes, from last to first. The forward repetition task involved 80 items (40 words, 40 pseudowords) presented in increasing length. The mean duration of stimuli for this task was .582 s ( $SD = .168$ ). For its own part, the backward

repetition task comprised 120 stimuli (40 words presented in typical order [e.g., *carta*, meaning ‘letter’], 40 words presented in reverse order [e.g., *efej* [for *jefe*], meaning ‘boss’], and 40 pseudowords [e.g., *baisa*]), also presented in increasing length.

The sets used for both directions contained 20 high-frequency words, with 10 short (1-2 syllables) and 10 long (3-6 syllables) items; 20 low-frequency words, with 10 short (1-2 syllables) and 10 long (3-6 syllables) items; 20 pseudowords composed of high-frequency syllables, with 10 short (2-3 syllables) and 10 long (4-5 syllables) items; and 20 pseudowords made up of low-frequency syllables, with 10 short (2-3 syllables) and 10 long (4-5 syllables). Additionally, the backward repetition task included another 40 words presented in reserve order, with 20 high-frequency and 20 low-frequency items. The use of increasingly long stimuli allowed examining the subjects’ reversing span. The mean duration of stimuli for task 2 was .631 s ( $SD = .194$ ).

The words used in the forward and backward tasks did not significantly differ in terms of mean frequency (log frequency; forward task:  $M = 1.34$ ,  $SD = .638$ ; backward task:  $M = 1.36$ ,  $SD = .633$ ) [ $t(118) = -.176$ ,  $p = .860$ ], familiarity (forward task:  $M = 5.52$ ,  $SD = .800$ ; backward task:  $M = 5.40$ ,  $SD = .877$ ) [ $t(118) = .727$ ,  $p = .469$ ], imageability (forward task:  $M = 4.90$ ,  $SD = 1.16$ ; backward task:  $M = 4.83$ ,  $SD = 1.29$ ) [ $t(118) = .291$ ,  $p = .772$ ] or concreteness (forward task:  $M = 4.89$ ,  $SD = 1.08$ ; backward task:  $M = 4.88$ ,  $SD = 1.10$ ) [ $t(118) = .042$ ,  $p = .966$ ]. Also, the frequency of high-frequency ( $M = 1.93$ ,  $SD = .284$ ) and low-frequency ( $M = .755$ ,  $SD = .164$ ) words was significantly different [ $t(94.23) = 27.76$ ,  $p < .001$ ]. Crucially, however, both lists were similar in familiarity [ $t(118) = 1.06$ ,  $p = .289$ ] and imageability [ $t(118) = -1.74$ ,  $p = .085$ ]. Pseudowords were extracted from a previous report (Aguado, 2005).

Each trial began with a white fixation cross appearing for 300 ms over a black screen, followed by the auditory stimulus (which was administered during the display of the black screen). The maximum response time given before the start of the following trial was 3 s for forward and 7 s for backward trials. Subjects’ responses were audio-recorded and then examined individually by one of the authors. Only responses that completely matched the expected answer (i.e., those that matched all the phonemes presented, in either forward or backward direction) were categorized as correct and given 1 point. Otherwise, responses were categorized as incorrect and given 0 points.

**Forward and backward sentence repetition:** The forward and backward sentence repetition tasks were used to assess phoneme sequencing ability in both normal and reserve order, but at the sentential level. Each of these tasks consisted of 25 sentences of increasing length (with five-trial sets comprising sentences of four, six, eight, ten, and 11-12 words).

The mean duration of stimuli for the two lists used in this task was 2.436 s ( $SD = .923$ ) for list 1 and 2.416 s ( $SD = .844$ ) for list 2. Here, too, the use of increasingly long sentences allowed assessing the subjects' reversing span. Sentences for both lists had similar grammatical structure (all were declarative, indicative, affirmative, unmarked, and endowed with one coordinated phrase), same number of words ( $n = 197$ ), frequency of contained words (log frequency; list 1:  $M = 2.70$ ,  $SD = .145$ ; list 2:  $M = 2.66$ ,  $SD = 1.50$ ) [ $t(392) = .323$ ,  $p < .747$ ] and mean number of phonemes in contained words (list 1:  $M = 4.60$ ,  $SD = 2.96$ ; list 2:  $M = 4.62$ ,  $SD = 2.95$ ) [ $t(392) = .034$ ,  $p < .973$ ]. section 2. In all analyses, alpha levels were set at  $p < .05$ .

**Lexical decision task:** This task was used to assess lexical access for words presented in regular or reverse order. It comprised 96 stimuli, namely: 24 words in normal order, 24 words in reverse order, and 48 pseudowords. Participants were instructed to press the “yes” key when a real word appeared on the screen (regardless of whether it was spelt forwards or backwards) and to press the “no” key when a pseudoword appeared. Stimuli remained on the screen for 300 ms and subjects had up to 2.5 s to respond. The inter-stimulus interval varied randomly between 1.5 and 2.5 s. Words written forward and backward were similar in mean frequency [ $t(45.54) = .863$ ,  $p = .393$ ], number of phonemes [ $t(46) = -.451$ ,  $p = .654$ ], familiarity [ $t(46) = -.948$ ,  $p = .348$ ], and imageability [ $t(46) = -.192$ ,  $p = .849$ ]. Pseudowords were created by changing one phoneme to each real-word stimulus. Performance was established by calculating the percentage of correct responses (accuracy) and response times (RTs).

## Neuroimaging data acquisition

MRI acquisition and preprocessing steps are reported following guidelines from the Organization for Human Brain Mapping (OHBM) (Nichols et al., 2017; Poldrack et al., 2017). Whole-brain T1-weighted anatomical 3D scans, spin echo volumes, were acquired in a 1.5-T Phillips Intera scanner with a standard eight-channel head coil. Scans were acquired parallel to the plane connecting the anterior and posterior commissures. The acquisition parameters used were: repetition time (TR) = 7.489 ms; echo time (TE) = 3.420 ms; flip angle = 8°; 196 slices, matrix dimension = 256 × 240; voxel size = 1 × 1 × 1 mm<sup>3</sup>; sequence duration = 7 min. Additionally, diffusion tensor images (DTI) were acquired with a twice-refocused, single-shot, echo-planar imaging pulse sequence. The tensor was computed using 32 non-collinear diffusion directions ( $b = 800$  s/mm<sup>2</sup>) that were maximally spread by considering the minimal energy arrangement of point charges on a sphere, and one scan without diffusion weighting ( $b = 0$  s/mm<sup>2</sup>,  $b_0$ ). Finally, we acquired functional MRI resting-



state recordings with 33 axial slices (5-mm thick). Functional spin echo volumes were registered in sequential ascent, parallel to the anterior-posterior commissures, covering the whole-brain, with the following parameters: TR = 2.777 ms; TE = 50 ms; flip angle = 90; 33 slices, matrix dimension =  $64 \times 64$ ; voxel size in plane =  $3.6 \text{ mm} \times 3.6 \text{ mm}$ ; slice thickness = 4 mm; sequence duration = 10 min; number of volumes = 209. Participants were asked to keep their eyes closed and to avoid moving or falling asleep during the acquisition of the functional volumes.

The two backward speakers underwent the complete scanning session. Structural (T1-weighted) images were obtained from all 24 controls, while diffusion tensor image (DTI) and resting-state functional connectivity (rsFC) recordings could be obtained only for 18 and 15 of them, respectively. Importantly, the control group used for each analysis remained sociodemographically matched with both subjects (for more details, see *Supplementary information*, section 1).

## **Neuroimaging analyses**

### **Whole-brain voxel-based morphometry (VBM)**

Whole brain voxel-based morphometry (VBM) was used to quantify differences in grey matter volume between each backward speaker and the control group (Ashburner & Friston, 2000). Preprocessing analyses were performed using the computational anatomy toolbox (CAT12: <http://www.neuro.uni-jena.de/cat/>) for the Statistical Parametric Mapping (SPM12: <http://www.fil.ion.ucl.ac.uk/spm/>) software, running on Matlab (2016b). First, all T1 weighted images were manually reoriented to set the origin to the anterior commissure using the Reorient function from SPM12. Then, the standard preprocessing pipeline of CAT12 was used. Briefly T1-weighted images were segmented, corrected for signal inhomogeneity and normalized using the Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL). Then, the corresponding normalization parameters were applied to the segmented gray matter images. Subsequently, the resulting gray matter normalized images were modulated by their Jacobian determinants and spatially smoothed (FWHM = 10 mm), which allow direct comparison of regional differences in the volume of gray matter volume (Mechelli, Price, Friston, & Ashburner, 2005). The total intracranial volume (TIV) was calculated as the sum of the gray matter, white matter, and cerebrospinal fluid. Finally, images were visually inspected.

Statistical analyses were performed on Matlab (2016b). First, the TIV of each participant was regressed out from the intensity of each voxel of the smoothed grey matter images. The residual of this analysis was used for the statistical analysis. A Crawford *t*-test

was used to compare the intensity of the calculated residual images of each of the two backward speakers with the control group. Results are reported with an uncorrected threshold of  $p < .001$  and a minimum cluster threshold of 50 continuous voxels, as previously reported (Kanai, Feilden, Firth, & Rees, 2011; Machino et al., 2014).

### **Tractography: Automatic fiber quantification (AFQ)**

#### **Diffusion tensor imaging (DTI) preprocessing**

DTI preprocessing started by correcting for head motion and eddy current distortions through the FMRIB Diffusion Toolbox (FDT), followed by brain extraction via the Brain Extraction Tool (BET; Smith, 2002) –both toolboxes are part of the FMRIB Software Library (FSL 5.0.1; [www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/); Jenkinson et al., 2012). Reconstruction of the diffusion tensor was carried out using least-square estimation algorithm included in the Diffusion Toolkit (Tractvis software, Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). Whole-brain tractography used an angular threshold of 35 degrees and an FA threshold of 0.15. Finally, fractional anisotropy (FA) maps were generated using Diffusion Toolkit for each subject.

#### **Automatic dissection of white matter pathways**

Automatic virtual dissections were performed using Automated Fiber Quantification software (AFQ, <https://github.com/jyeatman/AFQ>) (Yeatman, Dougherty, Myall, Wandell, & Feldman, 2012). Previous studies have shown that automatic dissection using AFQ shows high agreement with manual dissection of the white matter tracts (Ripollés et al., 2017; Vaquero, Rodríguez-Fornells, & Reiterer, 2016), while affording measures in 100 points along the tracts. Different white matter tracts were selected as pathways of interest due to their implication in phonological processing. Specifically, the three segments of the AF (long, anterior, and posterior) were dissected as dorsal language pathways (Catani, Jones, & Ffytche, 2005); while the IFOF, the UF, and the ILF were dissected as ventral language pathways (Dick et al., 2014). All tracts were dissected in native space and in both cerebral hemispheres.

The FA maps of BS1, BS2, and the control group ( $n = 18$ ) were imported into the AFQ software package, running in Matlab (2016b). AFQ processing was implemented following a standard pipeline mainly consisting in three steps (Yeatman et al. 2012). First, whole-brain tractography was created via a deterministic algorithm with a fourth Runge-Kutta path integration method and 1-mm fixed step size (Mori, Crain, Chacko, & Van Zijl, 1999). Second, tracts were segmented targeting two regions of interest (ROIs) defined in MNI

standard space. Only fibers passing through the two ROIs were assigned to a specific tract. Finally, tract refinement was performed in two steps: initially, the dissected tracts were compared, for each subject, with a probabilistic atlas of white matter tracts (Hua et al., 2008), and aberrant streamlines were discarded; then, a filter was applied establishing that streamlines that were spatially deviated 4 *SDs* from the core tract were removed. Thereupon, mean diffusivity (MD) and FA were calculated at 100 equidistant nodes along each of the six tracts of interest in each hemisphere. FA and MD are non-specific global indexes of diffusion. FA reflects the directionality coherence of water molecule diffusion, and it is considered an index of microstructural white matter integrity sensitive to factors such as axonal integrity and density, extent of myelination, fiber diameter, and fiber packing (Beaulieu, 2002; Pierpaoli & Basser, 1996). MD reflects the magnitude of diffusion; thus, higher MD values mean higher diffusivity. Generally, lower fiber integrity is characterized by decreased FA and increased MD, although this is likely an oversimplification (Soares, Marques, Alves, & Sousa, 2013). In addition, given that MD is calculated as the mean of the three eigenvalues of the diffusion tensor, when significant differences in MD between backward and controls were found, we looked at axial (AD) and radial diffusivity (RD) in these nodes in order to better distinguish the underlying source of variability. This allowed us to study the statistically significant differences between each backward speaker and the controls in any part of the white matter microstructure, making point-by-point comparisons along the tract. Comparisons between the subjects and the control group were performed using Crawford's two-tailed *t*-test. In order to avoid reporting false positives due to the high number of comparisons (i.e., 12 tracts), Bonferroni correction for multiple comparisons was applied. Therefore, significant differences were reported at  $p < .00416$ . Given that we looked at 100 nodes for each tract, an additional cluster correction was applied such that only clusters containing at least 5 continuous significant nodes (at  $p < .00416$ ) were reported (see Banfi et al., 2019 for a similar approach).

### **Seed-to-voxel resting-state functional connectivity (rsFC) analysis**

Resting-state fMRI data and the T1-weighted images of the backward speakers and the control group ( $n = 15$ ) were preprocessed on SPM12 following a standard preprocessing pipeline. The preprocessing steps included: AC-PC orientation for the functional and the T1-weighted images, realignment of the functional volumes to the first volume, coregistration between the functional and the structural T1-weighted image, segmentation of the T1-weighted image into different tissues, normalization of the functional and structural images to the MNI space using the parameters derived from the segmentation of the T1-weighted

image, and smoothing of the functional volumes with an 8-mm full-width half-maximum kernel.

RsFC analyses were performed with the CONN functional connectivity toolbox v.18a ([www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn), Whitfield-Gabrieli & Nieto-Castanon, 2012), through a gold-standard seed-to-voxel approach (Cole, Smith, & Beckmann, 2010). Normalized and smoothed functional data were band-pass filtered (0.008-0.09Hz) to remove low-frequency drift and high-frequency noise effects. The mean timeseries from each seed ROI was used as a predictor in a multiple regression model at each voxel of the brain. Different confound regressors were also included in the model to remove non-interest signals associated to cerebrospinal fluid, white matter, head movement (six motion correction parameters derived from the realignment preprocessing step), and scrubbing. CONN computed the Fisher-transformed bivariate correlation coefficients between the fMRI signal in each ROI (averaged across all voxels within the ROI) and every voxel of the brain, resulting in a connectivity map that represents all other voxels that are correlated with the seed ROI. The seed ROIs were 6-mm spheres selected from the ROIs available in the CONN toolbox, based on the FSL anatomical atlas. The selected ROIs and the coordinates of the center of the spheres were: left IFG pars triangularis (-50, 29, 9), right IFG pars triangularis (52, 28, 8), left IC (-37, 2, 1), right IC (38, 3, -1), left SMG (-60, -39, 31), right SMG (62, -35, 32), left pSTG (62, -24, 2) and right pSTG (-63, -30, 4). The ROIs selected as seeds for the seed-to-voxel analysis corresponded to brain areas known to be involved in phoneme sequencing, phonological encoding, and speech production (Baldo, Wilkins, Ogar, Willock, & Dronkers, 2011; Gow & Nied, 2014; Hickok & Poeppel, 2007; Siok, Jin, Fletcher, & Tan, 2003; Ueno & Lambon Ralph, 2013; Vaden, Piquado, & Hickok, 2011).

Functional connectivity maps for each seed ROI were used for second-level analysis based on one-way ANCOVAs with age as a covariate, as implemented in the CONN toolbox, in order to study differences between each subject and the control group. Since analysis were performed for eight seeds (four in each hemisphere), cluster-level FDR correction was adjusted to  $p < .00625$  in order to diminish family-wise error rate. This resulted from dividing .05  $\alpha$ -value by the eight tested seeds (i.e., Bonferroni correction). Thereby, results are reported using a whole-brain cluster-level FDR correction ( $p < .00625$ ) for voxel-wise analyses at  $p < .001$  (uncorrected) (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994).

## Results

### Behavioral results

## General cognitive tasks

**Reasoning test:** No significant differences were observed between the backward speakers and the control group (BS1: Crawford's  $t$ , two-tailed = .360;  $p$  = .723; BS2: Crawford's  $t$ , two-tailed = -1.79;  $p$  = .091).

**Memory tasks:** Results from the forward digit span task revealed that, relative to controls, performance was higher for BS1 (Crawford's  $t$ , two-tailed = 4.67;  $p$  < .001) and similar for BS2 (Crawford's  $t$ , two-tailed = -.386;  $p$  < .704). As regards backward digit span, no significant differences were observed between each subject and controls (BS1: Crawford's  $t$ , two-tailed = 1.76;  $p$  = .095; BS2: Crawford's  $t$ , two-tailed = -.133;  $p$  = .895).

**Operational span task:** Three subjects from the control group were excluded from data analysis because they failed to reach the minimum performance level of 85% on the math operations. Both backward speakers successfully reached the criterion. BS1 did not significantly differ from controls in either correctly recalled items (Crawford's  $t$ , two-tailed = .379;  $p$  = .710) or math errors (Crawford's  $t$ , two-tailed = .503;  $p$  = .622). For his part, compared with controls, BS2 recalled fewer items (Crawford's  $t$ , two-tailed = -3.71;  $p$  = .002) but did not differ in the number of math errors (Crawford's  $t$ , two-tailed = -.951;  $p$  = .357).

**Symmetry span task:** One subject from the control group was excluded from data analysis because he failed to reach the 85%-accuracy criterion on the symmetry judgement trials. Both backward speakers successfully reached the criterion. Relative to controls, BS1 showed similar performance in both correctly recalled positions (Crawford's  $t$ , two-tailed = .629;  $p$  = .538) and symmetry errors (Crawford's  $t$ , two-tailed = .313;  $p$  = .758). Instead, BS2 showed lower performance in correctly recalled positions (Crawford's  $t$ , two-tailed = -2.51;  $p$  = .023), with no differences in the rate of symmetry errors (Crawford's  $t$ , two-tailed = 1.01;  $p$  = .323). For more statistical details, see *Supplementary information*, section 2 (Table S1).

## Backward and forward language tasks

**Forward and backward word and pseudoword repetition:** Results from forward repetition revealed no significant differences between the backward speakers and controls for both words (BS1: Crawford's  $t$ , two-tailed = .000;  $p$  = 1; BS2: Crawford's  $t$ , two-tailed = .487;  $p$  = .500) or pseudowords (BS1: Crawford's  $t$ , two-tailed = .893;  $p$  = .384; BS2: Crawford's  $t$ , two-tailed = .000;  $p$  = 1) (Figure 1, panel A1). Conversely, backward repetition revealed higher accuracy for the two backward speakers than controls in all stimulus types, namely: words presented forwards (BS1: Crawford's  $t$ , two-tailed = 5.19;  $p$  < .001; BS2: Crawford's  $t$ , two-tailed = 5.94;  $p$  < .001), words presented backwards (BS1: Crawford's  $t$ ,

two-tailed = 5.73 ;  $p < .001$ ; BS2: Crawford's  $t$ , two-tailed = 4.87;  $p < .001$ ), and pseudowords (BS1: Crawford's  $t$ , two-tailed = 15.72;  $p < .001$ ; BS2: Crawford's  $t$ , two-tailed = 11.48;  $p < .001$ ) (Figure 1, panel B1). For more statistical details, see *Supplementary information*, section 2 (Table S2 and Table S3).

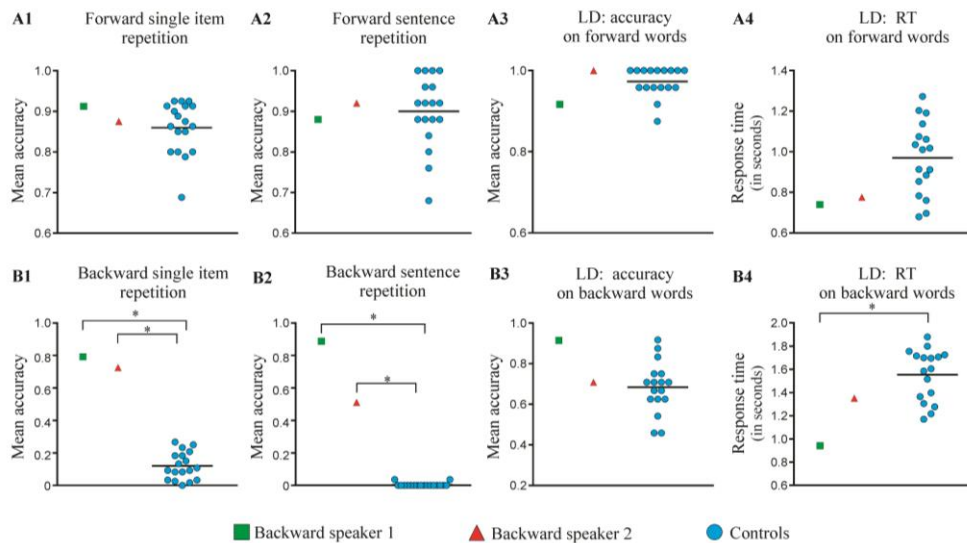
Further analyses were performed including each of the four memory tasks as covariates (i.e., forward and backward digit span and the operational and symmetry span tasks). All results remained significant (i.e., higher accuracy for backward speakers) after controlling for covariables (i.e., memory tasks) –for more statistical details, see *Supplementary information*, section 2 (Table S4).

**Forward and backward sentence repetition:** Results of forward sentence repetition revealed no accuracy differences between the two backward speakers and controls (BS1: Crawford's  $t$ , two-tailed = -.221;  $p = .827$ ; BS2: Crawford's  $t$ , two-tailed = .221;  $p = .827$ ) (Figure 1, panel A2). Contrariwise, backward sentence repetition proved significantly more accurate for both BS1 (Crawford's  $t$ , two-tailed = 65.58;  $p < .001$ ) and BS2 (Crawford's  $t$ , two-tailed = 41.63;  $p < .001$ ) (Figure 1, panel B2). In fact, the control group showed a floor effect, with only two participants being able to reverse only one short (three-word) sentence. For more statistical details, see *Supplementary information*, section 2 (Table S2 and Table S3).

Further analyses were performed including each of the four memory tasks as covariates. The accuracy of both subjects was still significantly higher than that of the control group when controlling for memory capacity –for statistical details, see *Supplementary information*, section 2 (Table S4).

**Lexical decision task:** Accuracy for words written in forward direction did not differ between controls and either BS1 (Crawford's  $t$ , two-tailed = -1.35;  $p = .195$ ) or BS2 (Crawford's  $t$ , two-tailed = .810;  $p = .429$ ) (Figure 1, panel A3). Similarly, neither subject had significant differences in RT (BS1: Crawford's  $t$ , two-tailed = -1.23;  $p = .235$ ; BS2: Crawford's  $t$ , two-tailed = -1.07;  $p = .300$ ) (Figure 1, panel A4). Accuracy was also similar for words written backward between controls and both BS1 (Crawford's  $t$ , two-tailed = -1.83;  $p = .084$ ) and BS2 (Crawford's  $t$ , two-tailed = .230;  $p = .821$ ) (Figure 1, panel B3). Contrarily, RT was lower for BS1 (Crawford's  $t$ , two-tailed = -2.67;  $p = .016$ ) but not for BS2 (Crawford's  $t$ , two-tailed = -.880;  $p = .391$ ) (Figure 1, panel B4). Finally, accuracy for pseudowords did not differ between controls and either subject (BS1: Crawford's  $t$ , two-tailed = 1.74;  $p = .099$ ; BS2: Crawford's  $t$ , two-tailed = .759;  $p = .458$ ). Still, this condition yielded lower RT for BS1 (Crawford's  $t$ , two-tailed = -2.13;  $p = .048$ ) but not for BS2 (Crawford's  $t$ ,

two-tailed = -1.42;  $p = .174$ ). For more statistical details, see *Supplementary information*, section 2 (Table S5).



**Figure 2.** Behavioral results. The figure shows outcomes for the two backward speakers and controls in the repetition (tasks 1-4) and lexical decision (LD) tasks, both in forward (A1, A2, A3, A4) and backward (B1, B2, B3, B4) direction. The asterisk (\*) indicates significant differences at  $p < .05$ .

## Neuroimaging results

### Whole-brain voxel-based morphometry (VBM) analysis

Results from the whole-brain VBM analysis revealed areas of significantly greater grey matter volume in both backward speakers compared to controls ( $p < .001$ , uncorrected; extent threshold = 50 voxels). No significant areas with lower grey matter volume were identified. For BS1, this effect was found in a cluster over the boundary between the left parahippocampal cortex and the FFG (Figure 2A). For BS2, significantly greater grey matter volume was found in several clusters, spanning the bilateral MFG and IFG, the right precuneus, and the right cuneus (Figure 3A) –for details, see *Supplementary information*, section 2 (Table S6 and S7).

### Tractography results: Automatic Fiber Quantification (AFQ)

Diffusion analysis using AFQ revealed significant differences between both backward speakers and the control group in MD (see Tables S8 and S9). Differences in FA are not reported as they did not survive the cluster correction –arguably because FA requires larger samples than MD to capture significant effects (De Santis, Drakesmith, Bells, Assaf, & Jones, 2014). Figures 2B and 3B show the studied tracts for BS1 and BS2, respectively. Relative to controls, BS1 showed higher MD values in the left and right posterior AF (Figure

2C). For his part, compared with controls, BS2 exhibited increased MD in the left posterior AF and the right UF (Figure 3C) – for details, see *Supplementary information*, section 2 (Table S8 and S9).

In order to further explore the nature of the differences in MD, we explored the patterns of AD and RD in the significant MD clusters. On the one hand, nodes of significant greater MD in the left posterior AF segment of BS1 compared to control showed higher RD than AD values. Figure 2C illustrates this pattern, where the MD (black line) increases in parallel to RD (blue dotted line) in the red shadowed area. The same pattern was seen in the significant MD cluster found for this subject in the right AF posterior segment (see in Figure 2C the corresponding plot for the right AF posterior segment). On the other hand, and in the same line, in the BS2, the statistically significant increase in MD found for the left AF posterior segment was accompanied by an increase in RD (as illustrated in Figure 3 C, left panel). Contrary, in the right UF the increase in MD (Figure 3C, right panel, red shadowed area) occurred together with an increase in AD while RD remained low.

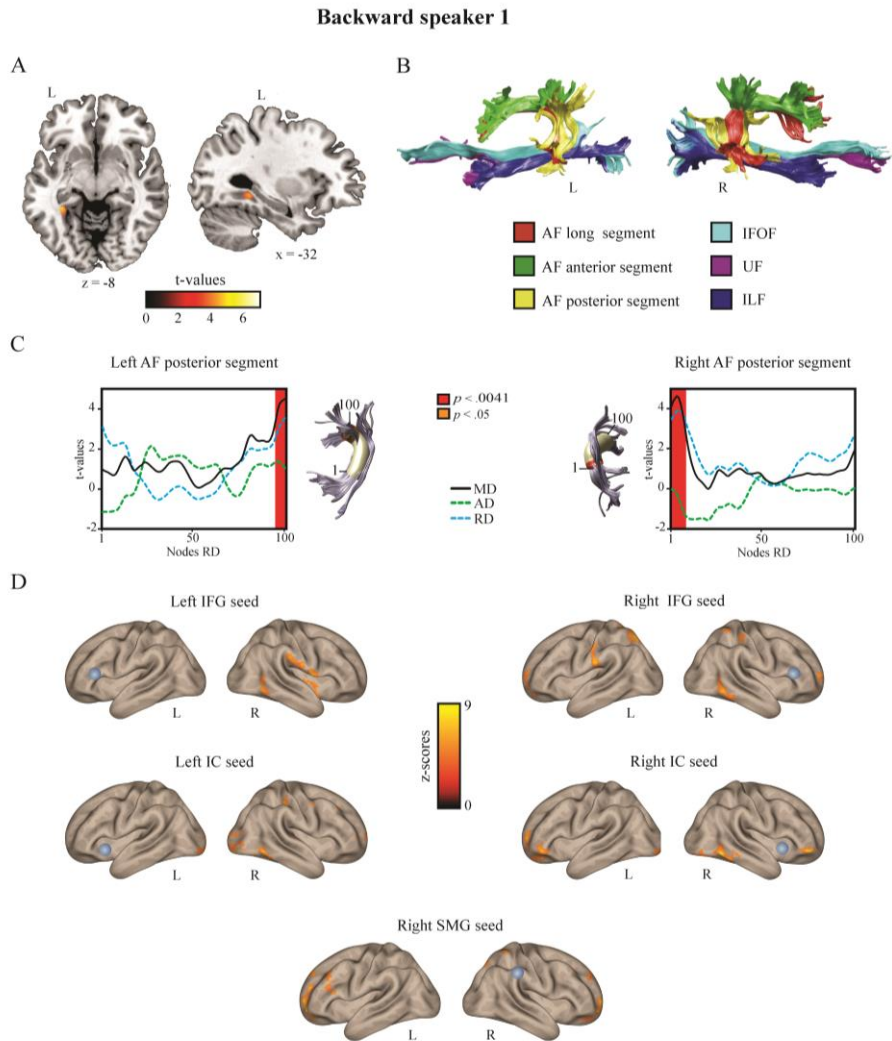
### **Seed-to-voxel resting-state functional connectivity (rsFC) analysis**

Results revealed significant differences in functional connectivity between each backward speaker and the control group. For BS1, greater connectivity was found between five seeds and several brain areas (Figure 2D) –for details, see *Supplementary information*, section 2 (Table S10). No seeds were found with significantly decreased functional connectivity. Specifically, compared to controls, BS1 exhibited increased connectivity of (i) the left IFG seed with right dorsal and ventral areas, including part of the SMG, IC, premotor ventral area, MTG and ITG; (ii) the right IFG seed with domain-general areas including bilateral parietal, anterior frontal, anterior cingulate and precuneus cortex, in addition to the right MTG and ITG; (iii) the left IC seed with bilateral occipital cortex, bilateral anterior frontal cortex, right cerebellum and right ITG; (iv) the right IC seed with bilateral frontal areas and right posterior ITG; and (v) the right SMG seed with bilateral anterior frontal areas, left MFG and IFG. No significant differences between BS1 and controls were found for the seeds located in the right or left posterior STG, or the left SMG.

BS2 also showed greater connectivity, relative to controls, between specific seeds and, mostly, with associative visual posterior regions (Figure 3D) –for details, see *Supplementary information*, section 2 (Table S11). Specifically, stronger connectivity was found between (i) the left IC seed and large clusters involving the left pSTG and bilateral lateral occipital cortex and cuneus; (ii) the right IC seed and the right inferior lateral occipital cortex and bilateral cuneus; and (iii) the left SMG seed and the left occipital pole. Also,



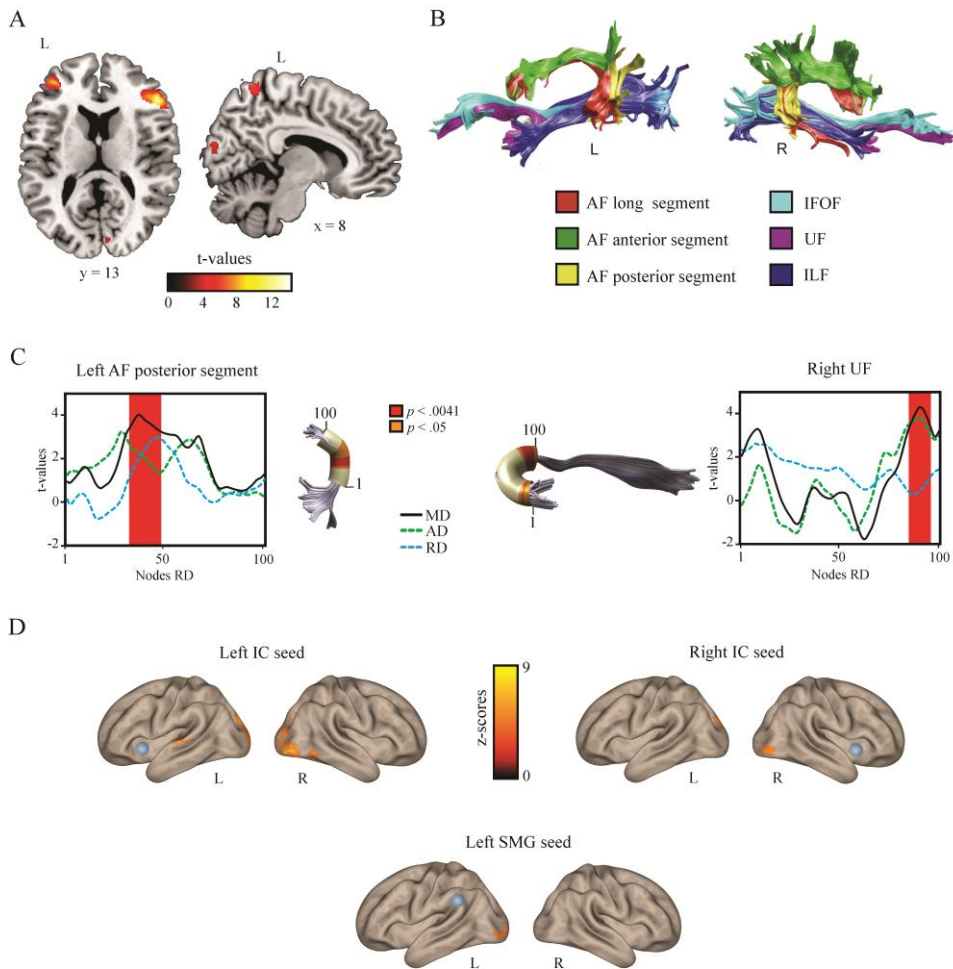
decreased connectivity was observed between the left IC seed and clusters involving the left cerebellum. No further significant differences were found.



**Figure 3.** Structural and functional neuroimaging results from Backward speaker 1. **A.** Voxel-based morphometry (VBM) results. Relative to controls, Backward speaker 1 showed significantly greater grey matter volume (red-yellow colors) in the left parahippocampal and fusiform gyri. The color bar represents  $t$ -values. Images are shown in standard space over a MNI template available in MRICRON software. **B.** Deterministic tractography reconstruction of the dorsal and ventral language white matter tracts in Backward speaker 1, in the left and right hemispheres, in native space. **C.** Profiles of tracts showing nodes with significantly different mean diffusivity (MD) in Backward speaker 1 compared to controls (red shadowed areas). The black solid line represents MD. Note that nodes with significant greater MD also show increments in radial diffusivity (RD, dotted blue line) but not in axial diffusivity (AD). Nodes are ordered in the dorsal-ventral direction. Tracts are shown using a three-dimensional rendering derived from Automated Fiber Quantification (AFQ) software, depicting a core fiber represented as a 5-mm-radius tube (color-coded based on  $p$ -values at each node along the tract). **D.** Seed-to-voxel functional connectivity results. Orange-yellow color indicates voxels showing increased functional connectivity with the seed in Backward speaker 1 compared to controls. The seeds are indicated for each analysis with a blue sphere. L: left; R: right; IFG: inferior frontal gyrus; IC: insular

cortex; SMG: supramarginal gyrus; AF: arcuate fasciculus; IFOF: inferior fronto-occipital fasciculus; UF: uncinated fasciculus; ILF: inferior longitudinal fasciculus.

### Backward speaker 2



**Figure 4.** Structural and functional neuroimaging results from Backward speaker 2. **A.** Voxel-based morphometry (VBM) results. Relative to controls, Backward speaker 2 showed significantly greater grey matter volume (red-yellow colors) in the left inferior and middle frontal gyri and in the right inferior frontal gyrus. The color bar represents *t*-values. Images are shown in standard space over a MNI template available in MRICRON software. **B.** Deterministic tractography reconstruction of the dorsal and ventral language white matter tracts in Backward speaker 2, in the left and right hemispheres, in native space. **C.** Profiles of tracts showing nodes with significant different mean diffusivity (MD) in Backward speaker 2 compared to controls (red shadowed areas). The black solid line represents MD. Note that for the left posterior AF nodes with significantly greater MD also show increments in radial diffusivity (RD, dotted blue line). The right UF nodes with significantly greater MD display higher axial diffusivity (AD; dotted green line). Nodes are ordered in the dorsal-ventral direction for the AF posterior segment and in ventral-dorsal direction for the UF. Tracts are shown using a three-dimensional rendering derived from Automated Fiber Quantification (AFQ) software, depicting a core fiber represented as a 5-mm-radius tube (color-coded based on *p*-values at each node along the tract). **D.** Seed-to-voxel functional connectivity results. Orange-yellow color indicates voxels showing increased functional connectivity with the seed in Backward speaker 2 compared to controls. The seeds are indicated for each analysis with a blue sphere. L: left; R: right; IC: insular cortex; SMG: supramarginal

gyrus; AF: arcuate fasciculus; IFOF: inferior fronto-occipital fasciculus; UF: uncinated fasciculus; ILF: inferior longitudinal fasciculus.

## Discussion

This study examined neurocognitive correlates of expertise in backward speech as a window into the mechanisms subserving phonological encoding, in general, and phoneme sequencing, in particular. Converging data from behavioral, structural and functional connectivity analyses consistently pointed to components of the dorsal stream (with complementary involvement of ventral, domain-general, and associative-visual mechanisms) as key signatures of elevated phoneme sequencing skills. These results illuminate an understudied dimension of phonological-phonetic encoding while informing models of language-related expertise.

Relative to controls, both subjects had significantly higher accuracy in all backward repetition tasks, with BS1 also exhibiting faster recognition of reversed written words. Considering that neither subject showed advantages in any of the forward repetition tasks, this confirms that they were specifically gifted for (re)sequencing of phonemes rather than other general phonological operations. Importantly, too, this selective advantage for backward speech remained significant after covarying for WM outcomes, indicating that the subjects' behavioral superiority was likely driven by phonological skills proper rather than by memory abilities, as described for other cases (Prekovic et al., 2016). In line with evidence from other models of expert language processing (Santilli et al., 2019; Yudes, Macizo, Morales, & Bajo, 2013), this finding suggests that linguistic enhancements due to recurring practice may emerge only for specifically taxed functions, irrespective of other domain-general skills (García, Muñoz, & Kogan, 2019). Furthermore, greater accuracy in reversing tasks may partly reflect the subjects' learning of (reversed) phoneme sequences, such that their processing as chunks (Segawa, Masapollo, Tong, Smith, & Guenther, 2019) would lower memory demands.

These behavioral advantages were accompanied by specific structural and functional brain patterns. Interestingly, beyond some commonalities, each backward speaker presented distinct neural signatures, suggesting that similar behavioral advantages may result from different plastic adaptations (or from distinctive pre-existing differences) which, in turn, may reflect contrastive underlying strategies (Noppeney, Friston, & Price, 2004).

Regarding volumetric differences, comparisons with controls revealed greater grey matter volume in the parahippocampal/fusiform gyri for BS1 and in the bilateral MFG and IFG, right precuneus, and right superior parietal cortex for BS2. The

parahippocampal/fusiform gyri are involved not only in episodic memory and visuospatial processing (Aminoff, Kveraga, & Bar, 2013), but also in successful verbal memory encoding (Strange, Otten, Josephs, Rugg, & Dolan, 2002) and working memory processing (Bergmann, Rijpkema, Fernández, & Kessels, 2012). Tentatively, this might constitute a substrate mediating BS1's greater memory capacity, reflected by his ability to manipulate larger amounts of phonological information –as suggested by his higher performance in reversal of long sentences compared to BS2, and his greater digit span compared to controls. As regards in BS2, some of the regions presenting increased grey matter volume, such as the bilateral IFG, are critical hubs for phonological-phonemic encoding and articulatory planning (Ferpozzi et al., 2018; Flinker et al., 2015; Siok, Jin, Fletcher, & Tan, 2003; Zatorre, Meyer, Gjedde, & Evans, 1996), actually exhibiting increased activation during backward compared to forward speech in expert subjects (Prekovic et al., 2016). Additionally, greater volume in the right cuneus and precuneus might suggest an additional involvement of attentional and visual imagery processes in this skill (Cavanna & Trimble, 2006; Corbetta, Kincade, & Shulman, 2002).

As regards white matter differences, both backward speakers depicted greater MD in parts of the temporo-parietal segment of the AF, seemingly reflecting greater perpendicular diffusivity (i.e., RD). Of note, the posterior segment of the AF connects two critical hubs of the phonological network: the posterior STG and the inferior parietal cortex (including the SMG) (Catani et al., 2005). Thus, this result hints to a possible link between the structural configuration of this dorsal tract and phoneme reversal skills. Furthermore, the posterior segment of the AF reaches posterior inferior and middle temporal areas implicated in orthographic-phonological decoding processes (i.e., word-form area) (Thiebaut De Schotten, Cohen, Amemiya, Braga, & Dehaene, 2014) and in phonological-semantic mappings (i.e., lexical interface) (Hickok & Poeppel, 2007), respectively. Thus, two plausible interpretations may be inferred. First, the distinctive AF pattern observed in both subjects may reflect increased recruitment of the graphemic-phonemic translation circuit (Broce et al., 2019; Thiebaut De Schotten et al., 2014), sustaining speech reversal through visualization of the to-be repeated stimuli. Second, backward speech may be further supported by direct activation of the reversed phonological sequence through prior activation of the semantic context during speech perception (Catani et al., 2005; Hickok & Poeppel, 2007). Yet, the latter is unlikely to be the only mechanism supporting this ability, since greater reversal abilities were also observed in meaningless words (i.e., pseudowords).

For his part, BS2 also exhibited significantly greater MD in part of the right UF, accompanied by increased AD. As part of the ventral pathway, the UF participates in

semantic processing, lexical retrieval (Basilakos et al., 2014; Papagno, 2011), and semantically constrained word learning (Ripollés et al., 2017). Tentatively, this could indicate that inverted words were accessed directly as full lexical units, as suggested above, although further research would be needed to test this conjecture. Yet, further explanations seem to be possible. The ventral pathway, beyond its crucial involvement in lexico-semantic access, has been implicated in monitoring functions required for the correct sequencing of phonemes during repetition of unfamiliar strings (Saur et al. 2009), suggesting that the observed difference may be explain by the increased monitoring demands placed by phoneme resequencing. Moreover, the ventral route can represent compensatory mechanisms when the dorsal stream is overloaded (Lopez-Barroso et al., 2011), not developed, or dysfunctional (Brauer, Anwander, & Friederici, 2011; Torres-Prioris et al., 2019). Therefore, the distinctive diffusion pattern found in the UF may be linked to the systematic recruitment of supporting ventral mechanisms upon continual and excessive demands placed by the backward speakers on dorsal routes. The fact that the observed pattern involved the right hemisphere may suggest individual differences in language organization, aligning with the greater cluster of grey matter volume in the right than in the left hemisphere found in this subject in our VBM analyses. As the UF is also considered a limbic tract (Catani & de Schotten, 2012; Von Der Heide, Skipper, Klobusicky, & Olson, 2013), its particular configuration in BS2 might also be partially associated to the motivational and rewarding value of language reversal, as described for language learning (Ripollés et al., 2014).

Accordingly, the structural differences identified in our subjects may represent putative signatures of their superior abilities for reversing phonological units. Most of these findings fit with previous evidence of structural brain changes associated with expert auditory-motor abilities. Indeed, professional simultaneous interpreters and phoneticians, who exhibit elevated phonemic processing abilities, also show grey matter volumetric increases (Becker, Schubert, Strobach, Gallinat, & Kühn, 2016; Golestani, Price, & Scott, 2011; Hervais-Adelman, Moser-Mercer, Murray, & Golestani, 2017; but see Elmer, Hänggi, & Jäncke, 2014) and lower FA associated to greater RD in networks mediating speech articulation and sensory-motor integration (Elmer, Hänggi, Meyer, & Jäncke, 2011). In fact, greater perpendicular diffusivity (i.e., lower FA and greater RD) in relevant pathways is a frequent finding in studies of expert auditory-motor abilities (Elmer et al., 2019; Elmer et al., 2011; Imfeld, Oechslin, Meyer, Loenneker, & Jancke, 2009; Vandermosten, Price, & Golestani, 2016). The observed MD adjustments in task-relevant tracts may be attributed to greater efficiency of these networks, potentially resulting from increased axonal caliber, sprouting of collateral branches or greater extracellular space (Beaulieu, 2009; Giacosa,

Karpati, Foster, Penhune, & Hyde, 2016; Vandermosten et al., 2016), affecting to some nodes of the tract. Still, current understanding of diffusion dynamics precludes any fine-grained conclusions in this regard (Beaulieu, 2002, 2009; Neil et al., 2002).

Additional insights come from our functional connectivity analyses. Compared with controls, both subjects showed greater coupling between phonologically relevant seeds and several areas involved in verbal, visual, and otherwise cognitive processing (Duncan & Owen, 2000; Koechlin, 2011). In particular, the two backward speakers presented enhanced connectivity between the left IC –implicated in articulation (Baldo, Wilkins, Ogar, Willock, & Dronkers, 2011; Dronkers, 1996) and auditory-motor integration (Mutschler et al., 2009)– and right occipito-temporal areas encompassing the FFG region. For BS1, this pattern was also seen for the left and right IFG seeds. Suggestively, given their involvement in orthographic processing, occipito-temporal areas have been proposed to mediate inner visualization strategies during expert backward speech (Prekovic et al., 2016). In fact, meta-analytic evidence attests to the involvement of the bilateral IC in receptive and expressive language processes (Chang, Yarkoni, Khaw, & Sanfey, 2013), whereas the FFG is critically engaged during phonologically demanding tasks (Dietz, Jones, Gareau, Zeffiro, & Eden, 2005) as well as phono-graphemic integration (Tan, Laird, Li, & Fox, 2005). Moreover, the FFG plays a crucial role in high-level visual processes, such as reading (McCandliss, Cohen, & Dehaene, 2003; Weiner & Zilles, 2016), and more critically, due to the increased cross-talk between FFG and phonological dorsal areas after literacy is attained, it is activated in a top-down manner by phonological stimuli in the absence of visual stimuli (Dehaene et al., 2010). Thus, this coactivation pattern might reflect greater integration between phonological-phonetic encoding and visual-orthographic processes –a possible implicit strategy underlying backward speech skills.

Furthermore, BS1 exhibited greater functional coupling between left seeds and several right-sided regions (including perisylvian and occipito-temporal areas), while right seeds showed both greater intra- and inter-hemispheric functional connectivity across perisylvian, parietal, and occipital regions. These patterns suggest, on the one hand, stronger synchrony in left-sided language-preferential regions (Friederici & Gierhan, 2013; Hickok & Poeppel, 2007) and phonologically sensitive right-sided hubs (Hartwigsen et al., 2010; Vigneau et al., 2011), pointing to greater involvement of the right hemisphere in phonological-phonetic encoding processes in BS1 compared to controls. On the other hand, generally, enhanced coupling in the fronto-temporo-parietal network (partially encompassing the dorsal and ventral streams) suggests strengthening of circuits involved in auditory-motor integration as well as maintenance and manipulation of verbal information in memory

(Froudish-Walsh, López-Barroso, Torres-Prioris, Crosson, & Berthier, 2017; Koenigs, Barbey, Postle, & Grafman, 2009; Majerus, 2013) –two crucial processes underlying language reversal. Indeed, increased coupling between auditory and articulatory areas has been observed in expert simultaneous interpreters, presumably reflecting elevated phoneme-to-articulation mapping skills (Elmer & Kühnis, 2016). Also, greater connectivity between phonology-related and domain-general areas (i.e., cingulate cortex, prefrontal and parietal areas) may reflect the high cognitive demands of continual backward speech (Fedorenko, Duncan, & Kanwisher, 2013).

For his part, BS2 exhibited greater coupling between bilateral seeds implicated in phonological processing and posterior areas involved in visual and graphemic processing (e.g., occipito-temporal cortex) (Carreiras, Armstrong, Perea, & Frost, 2014; Dehaene & Cohen, 2011). Conceivably, this hyperconnectivity pattern might represent a neural fingerprint of implicit visual imagery underlying speech reversal, as previously suggested by regional activation patterns during backward speech (Prekovic et al., 2016). This interpretation, in fact, fits well with the lack of exceptional memory abilities in BS2.

In sum, both convergent and divergent results across the two subjects suggest that expertise in phonological encoding (and, more particularly, phoneme sequencing) is mediated by structural and functional adaptations along the dorsal stream, with additional support from ventral, visual-associative and domain-general areas. This conclusion supports the dual-stream model of language processing (Hickok & Poeppel, 2007) while affording neurocognitive insights on expert language skills. For instance, anatomical and functional adjustment in networks mediating phonological, lexico-semantic, and language control processes have been repeatedly reported in simultaneous interpreters relative to untrained multilinguals (García et al., 2019; Hervais-Adelman & Babcock, 2019), and phoneticians relative to subjects without phonetics training (Golestani et al., 2011; Vandermosten et al., 2016). The present study extends such findings by showing that language-related neuroplastic adaptations may emerge even for unconventional forms of language expertise, even those that are not publicly used in daily life or honed through professional training.

Finally, as stated earlier, our study indicates that similar forms of language expertise may recruit differential neural mechanisms. Although the majority of the studies on language-related neuroplasticity have favored averaged reports across multiple samples, thus masking potential individual differences within their samples (Elmer et al., 2014; Elmer et al., 2019; Golestani et al., 2011; Vandermosten et al., 2016), our results align with few studies using difficult artificial language learning tasks in healthy subjects that report individual variability in the integrity of dorsal and ventral white matter tracts associated to successful learning

(Lopez-Barroso et al. 2013; Lopez-Barroso et al. 2011; Lopez-Barroso and De Diego-Balaguer 2017). Crucially, a recent study (Assaneo et al., 2019) has also provided evidence on individual variability in auditory-motor integration abilities, potentially related to the adoption of different cognitive strategies during linguistically demanding tasks. Compatibly, our results suggest that the similar forms of language expertise may rely on different neural signatures.

Less directly, our results may also have clinical implications, in particular for those disorders characterized by phonemic (or grapheme) phonological encoding or sequencing errors. For instance, conduction aphasics frequently manifest phonemic paraphasias involving phoneme substitution or displacement (Damasio & Damasio, 1980; Goodglass, 1992) –a pattern that is also observed in other aphasias types such as the logopenic variant of primary progressive aphasia (Gorno-Tempini et al., 2008; Kohn, 1992). In this sense, the identification of critical networks underlying phoneme sequencing skills may promote advances for the diagnosis, prognosis, monitoring, and treatment of such conditions –e.g., by foregrounding key neural targets for non-invasive brain stimulation protocols.

#### Limitations and avenues for further research

Its contributions notwithstanding, the present study presents some limitations. First, it is based on a small sample size, comprising only two subjects. Although single-case studies have proven crucial for understanding of brain-language relationships, in general (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Thiebaut de Schotten et al., 2015), and the neural bases of backward speech, in particular (Prekovic et al., 2016), future work should aim to replicate our findings in larger samples. Second, our design did not include *in vivo* neural correlates of backward expertise. Even though the results converge with those from task-related neuroimaging research on spontaneous backward speech (Prekovic et al., 2016), and despite the validity of off-line assessments to detect neural correlates of language expertise (Elmer et al., 2019; Golestani et al., 2011; Vandermosten et al., 2016), further investigations should complement our approach with ongoing neuroscientific data. Third, our cross-sectional design did not allow us to determine whether the neural patterns observed are the result of experience-dependent plastic changes due to training, or if they reflect pre-existing individual differences. Thus, longitudinal studies are required to shed light on this issue. Finally, due to practical limitations, behavioral and neuroimaging analyses were here performed on two separate samples, which precluded the exploration of correlations between performance and neural signatures. Although this methodology has yielded informative results regarding other



aspects of language (Steeb et al., 2018), it would be desirable to circumvent such a limitation in new studies.

## Conclusion

Our results suggest that expertise in backward speech, as a proxy of elevated phonemic sequencing skills, encompasses varied structural and functional adaptations along the dorsal stream, as well as in components of the ventral stream, visual, and otherwise cognitive processing areas. These findings inform current neurocognitive models of phonological encoding and constrain our understanding of language-related neuroplasticity at large. Further research along these lines may illuminate a hitherto underexplored aspect of verbal processing.

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## Supplementary information

### 1. Behavioral assessment

**Operational span task.** In this task letters are used as to-be-remembered stimuli and math operations as distractor. In each trial, participants viewed a letter and then performed a calculation. This sequence was repeated in sets of three to seven trials, varying randomly across participants, with a total of 75 trials. After each set, subjects were presented with an extended list of letters and had to click on the correct ones in their order of appearance. After the recall screen, a feedback screen showed the number of correctly remembered letters and the percentage of correct calculations. Prior to the task, all subjects underwent a three-stage training phase (for details, see Unsworth, Redick, Heitz, Broadway, & Engle, 2009). Also, during the math operation training, we calculated the mean time needed to solve the operations. If during testing subjects took more than the mean time plus 2.5 SDs, that trial was computed as a speed error. Scores were calculated by summing the number of letters recorded correctly and in the right order (number of correct responses) and summing up the number of mistakes in math operations (speed and accuracy), named math errors (Unsworth et al. 2005). Only subjects with a performance of 85% or higher in the math operations entered the analysis (Unsworth et al. 2005).

**Symmetry span task:** This test resembles the operational span task, with some differences. First, instead of letters, participants are presented with a four-by-four matrix in which different to-be remembered locations are signaled. The number of locations varied from two to five in each set, with a total of 42 trials. Second, instead of performing math operations, subjects had to judge whether a figure was symmetrical in its vertical axis or not. To this end, participants were shown sequences of spatial locations in the matrix, followed by a figure to judge its symmetry; this was followed by the testing phase. As in the operational span task, feedback was offered concerning the number of correct locations remembered and the percentage of correct answers in the symmetry judgement phase. Before testing, all participants completed three practice blocks allowing for familiarization with all phases of the task. Two scores were calculated, namely: the number of correct positions and of symmetry errors. The former was obtained by summing up the number of locations remembered correctly and in the right presentation order; the latter was established by adding the number of accuracy and speed errors committed in the symmetry judgment trials. The criterion to determine speed errors was the same as that used for the operation span task but based on the time employed in the symmetry judgment trials.

### Stimuli

#### *Forward word and pseudoword repetition task.*

Words forward (n=40)			
High-frequency words		Low-frequency words	
1-2 syllables	3-6 syllables	1-2 syllables	3-6 syllables
noche	conferencia	peine	mochila
sala	instituto	pipa	sátira
Llama	ejecución	soñar	manipular
juez	médico	cuco	deducir
monte	guitarra	clavo	concordia
avión	capacidad	sobra	ardilla
junta	inversión	truco	coyote
pleno	información	pala	abeja
presión	octubre	pliego	conejo
patria	constitución	dogma	demora

Pseudowords (n=40)							
High-frequency syllables				Low-frequency syllables			
2 syll.	3 syll.	4 syll.	5 syll.	2 syll.	3 syll.	4 syll.	5 syll.
ena	conamo	entosame	terablenicia	olu	burrefo	ustiñole	neciglotadia
cote	paesma	deteraco	cosimenlada	chegue	geoncu	denomugue	cosumanfora
esmo	asope	pacósená	indetomapo	osfu	irrolo	marópeno	anquibesido
saén	taensi	menciabiso	analícato	riol	muñeas	tundialaso	onotánego
decón	brénodi	autidenes	masperamones	bupil	plúzogue	augicumal	cusmipalates

**Backward word and pseudoword repetition task.**

Words forward (n=40)			
High-frequency words		Low-frequency words	
1-2 syllables	3-6 syllables	1-2 syllables	3-6 syllables
amor	solidaridad	blusa	apoyarse
fecha	argentina	pera	pereza
cuba	hospital	fiera	carruaje
hotel	hermano	ansia	cortina
pagar	protección	sentar	amargura
acto	existencia	trueno	escoba
carta	desarrollar	maldad	tortilla
curso	comisario	ciervo	bailarín
nación	ministerio	limbo	martillo
vigor	respiración	pulso	modernidad
Words backward (n=40)			
achul (Lucha)	nóisivelet (televisión)	kilo (olik)	zedarnoh (honradez)
efej (Jefe)	nóicisopxe (exposición)	ebleum (Mueble)	sateirotsih (historietas)
reac (Caer)	ainoloc (colonia)	opas (Sapo)	olugnátcer (rectángulo)
arim (Mira)	olucríc (círculo)	ralloc (Collar)	adalsne (ensalada)
rirba (Abrir)	nóisaerc (Creación)	nótob (botón)	agutrot (Tortuga)
nóinu (Unión)	akjgól (lógica)	atnam (manta)	anaznam (manzana)
evalc (Clave)	otisóporp (propósito)	azat (taza)	ogolónom (monólogo)
eplog (Golpe)	ovituceje (ejecutivo)	zeun (nuez)	orenillag (gallinero)
agrac (carga)	orejnartxe (Extranjero)	oidet (Tedio)	dadineres (serenidad)
apluc (Culpa)	ojabart (trabajo)	resoc (coser)	aimedipe (epidemia)

Pseudowords (n=40)							
High-frequency syllables				Low-frequency syllables			
2 syll.	3 syll.	2 syll.	3 syll.	2 syll.	3 syll.	2 syll.	3 syll.
mengo	diconcias	bacomputer	padestamendos	dentu	rijundios	fubelporón	dolirtagentas
bledos	meterción	atelación	senociaresca	clegas	gosandión	acichesión	fomosiarinda
pronda	camendo	grancodesta	aidespeconte	blismu	putelcho	prantecolde	aicaldisempa
baisa	prestona	perlitebles	elestramienda	zaiña	plasquice	yerguimeblos	esontrafielda
miendo	puesticón	maprósedas	prodalesciones	quieslo	luesbicán	mafrínegas	cletufansiolas

### ***Forward sentence repetition***

1. Iba andando y cayó
2. Estará lunes y martes
3. Abren escuelas y hospitals
4. Sabe leer y escribir
5. Colgar carteles y avisos
6. Hoy he comido pollo y papas
7. Lo operaron y se recuperó rápido
8. Las opciones parecen buenas y acertadas
9. Multan por alta velocidad y drogas
10. La lectura es gratificante y divertida
11. Aprobé todos los exámenes y pasé de año
12. En esta zona llueve en invierno y verano
13. Ha llegado esta mañana y regresa el sábado
14. Me podría haber llamado y no lo hizo
15. Presenta una obra apta para chicos y grandes
16. Pronto cumple cincuenta años y lo festejará a lo grande
17. La selección de películas incluye algunas clásicas y otras modernas
18. Las computadoras se usan para resolver problemas y para entretenerse.
19. Encima de mi escritorio está la carta y el sello
20. Pedile a la vecina un poco de leche y chocolate
21. Hubo varios heridos en un accidente y llamaron a la ambulancia
22. Son características típicas de los monos y de los humanos inteligentes
23. El ejercicio físico mejora la salud y el estado de ánimo general
24. El auto que me he comprado lleva termómetro y equipo de música
25. El cerebro controla funciones vitales y permite responder a estímulos externos

### ***Backward sentence repetition***

1. Inventar letras y cantar
2. Es atento y gracioso
3. Luna llena y playa
4. Apagamos y nos vamos
5. Cosas locas y aburridas
6. El escarabajo azul y la tortuga
7. Suena el teléfono y enseguida aparece
8. Esperando su paquete y el cambio

9. Su trabajo exige esfuerzo y paciencia
10. Hay empanadas al horno y canelones
11. Canciones que te traen recuerdos y te alegran
12. Me pidió permiso para salir y se fue
13. Mafalda es una niña muy inteligente y ocurren
14. El universo está formado por planetas y estrellas
15. El abogado sabe mucho de leyes y sentencias
16. El libro es ameno y cambiará tu forma de pensar
17. Es una idea genial y seguro que lo podés conseguir
18. Cuando era joven jugaba al trompo y a las bolillas
19. Pronto cumplirá su promesa y estaremos todos listos para festejar
20. Los avances tecnológicos han impulsado la industria y la comunicación
21. Los animales característicos de la sabana son la jirafa y el león
22. Las aves revolotean entre los presentes y se posan en las estatuas
23. El taxi paró tres cuadras después y todos bajaron de prisa
24. Todas las semanas salgo a correr y a andar en bicicleta
25. El departamento tiene cuatro habitaciones arriba y un patio amplio abajo

### *Lexical decision*

Words (n = 48)				Pseudowords (n = 48)			
roca	teléfono	gorriones	jarra	racu	tolófena	garriones	jurro
subir	teniente	lechuga	morder	sibor	taneinto	lichuzo	murdor
guión	imaginación	cerrojo	moño	goeún	imigenución	cerrrujo	muña
tela	solitario	zanahoria	loba	tile	sulitereo	zapatoria	lubo
pierna	fotografía	gaseosa	fresa	poerno	futogrefía	gesiosa	fruso
vaca	espejo	paella	jarrón	vocu	espaje	puello	jorrán
guardia	ceremonia	chorizo	clavel	gaurdio	cirumonea	churoza	cleval
regla	sabiduría	butaca	barman	rugle	sabudaría	botuca	bermon
sal	esfera	bromear	cartón	sil	esforo	brumeor	cartán
juicio	anillo	amabilidad	aula	joiceo	anulla	amobiludad	aola
cantar	médica	anotar	hacha	contur	mídeco	anuter	hucho
viaje	esquina	arruga	uña	veaja	esqueno	arragu	eña

### **Neuroimaging data acquisition**

Tractographic analyses were made with a control sample of 18 participants. This subsample was matched with both backward speakers in terms of age (Backward speaker 1: Crawford's *t*, two-tailed = .603; *p* = .554; Backward speaker 2: Crawford's *t*, two-tailed = 1.025; *p* = .319) and years of education (Backward speaker 1: Crawford's *t*, two-tailed = .926; *p* = .367; Backward speaker 2: Crawford's *t*, two-tailed = 0.00; *p* = 1).

Resting-state functional connectivity analyses included a control sample of 15 participants, who were also matched with both backward speakers in terms of age (Backward speaker 1: Crawford's *t*, two-tailed = .476; *p* = .641; Backward speaker 2: Crawford's *t*, two-tailed = .875; *p* = .396) and years of education (Backward speaker 1: Crawford's *t*, two-tailed = .602; *p* = .556; Backward speaker 2: Crawford's *t*, two-tailed = -.303; *p* = .767).

## 2. Supplementary results

**Table S2.** Accuracy of the two backward speakers and the control group in the performance of four repetition tasks.

Repetition direction	Stimulus type (dependent measure) [n = 18]	Controls (mean and SD)	Statistical comparison									
			BS1	BS2	t	P	zCC	CI	t	P	zCC	CI
<i>Forward and backward word and pseudoword repetition</i>												
Forward	Words	.95 (.04)	.95	.97	.000	1	.000	-.462 to .462	.487	.632	.500	.002 to .985
	Pseudowords	.77 (.109)	.87	.77	.893	.384	.917	.354 to 1.46	.000	1	.000	-.462 to .462
Backward	Words forward	.21 (.133)	.92*	1*	5.19	<.001	5.33	3.49 to 7.16	5.78	<.001	5.94	3.90 to 7.96
	Words backward	.13 (.112)	.79*	.69*	5.73	<.001	5.89	3.87 to 7.90	4.87	<.001	5.00	3.26 to 6.72
	Pseudowords	.030 (.039)	.66*	.49*	15.72	<.001	16.15	10.75 to 21.54	11.48	<.001	11.79	7.83 to 15.74
<i>Forward and backward sentence repetition</i>												
Forward	Sentences	.90 (.088)	.88	.92	-.221	.827	-.227	-.692 to .244	.221	.827	.227	-.244 to .692
Backward	Sentences	.004 (.013)	.88*	.56*	65.58	<.001	67.38	44.94 to 89.80	41.63	<.001	42.76	28.25 to 57.00

acc: accuracy. BS1: Backward speaker 1; BS2: Backward speaker 2. Statistical comparisons were performed through two-tailed Crawford's t-tests (Crawford & Howell, 1998; Crawford, Garthwaite, & Porter, 2010). Asterisks (\*) indicate significant differences at  $p < .05$ .

**Table S3.** Accuracy for the two backward subjects in the backward repetition tasks.

	BS1	BS2
Single items <sup>1</sup>		
1-word forward	.92	1
1-word backward	.79	.69
1-pseudoword	.66	.50
<b>Mean all items</b>	<b>.79</b>	<b>.73</b>
Sentences		
4-6 words	1	.90
10-12 words	.70	.30
<b>Mean all items</b>	<b>.88</b>	<b>.56</b>

<sup>1</sup> This task required backward repetition of words presented in forward position (prototypical form), words presented in backward order, and pseudowords. BS1: Backward speaker 1; BS2: Backward speaker 2.

**Table S4.** Comparison of the two backward speakers with controls in backward tasks, controlling for memory outcomes.

	Statistical comparison <sup>1</sup>					
	BS1 vs. controls			BS2 vs. controls		
	<i>p</i>	<i>z</i> CCC*	CI	<i>p</i>	<i>z</i> CCC*	CI
Backward repetition of words and pseudoword:	< .001	7.945	3.250 to 10.53	.001	7.15	2.99 to 9.41
Backward repetition of sentences	< .001	67.88	36.674 to 82.03	< .001	43.07	23.18 to 52.11

<sup>1</sup> Bayesian comparison developed to compared a single case's score to a control group when controlling for covariates (Crawford, Garthwaite, & Ryan, 2011). The BTDCov.ex was used. BS1: Backward speaker 1; BS2: Backward speaker 2. (\*) effect size.

**Table S5.** Performance of the two backward subjects and the control group in the lexical decision task.

Stimulus type and dependent measure ( <i>n</i> = 17)	Controls (mean and <i>SD</i> )	Statistical comparison									
		BS1	BS2	<i>t</i>	<i>p</i>	<i>zCC</i>	CI	<i>t</i>	<i>p</i>	<i>zCC</i>	CI
Global accuracy	.79 (.08)	.95	.85	1.94	.069	2.00	1.15 to 2.82	.729	.476	.750	.200 to 1.28
Global RT	1.44 (.257)	.920	1.12	-1.98	.064	-2.04	-2.88 to -1.18	-1.199	.248	-1.23	-1.86 to -.586
Forward accuracy	.97 (.036)	.92	1	-1.35	.195	-1.38	-2.05 to -.705	.810	.429	.833	.269 to 1.37
Forward word RT	.969 (.179)	.742	.772	-1.23	.235	-1.26	-1.90 to -.613	-1.07	.300	-1.10	-1.69 to -.483
Backward accuracy	.68 (.127)	.92	.71	1.83	.084	1.89	1.07 to 2.68	.230	.821	.236	-.250 to .715
Backward word RT	1.55 (.222)	.939*	1.35	-2.67	.016	-2.75	-3.80 to -1.68	-880	.391	-905	-1.46 to -.327
Pseudoword accuracy	.75 (.128)	.98	.85	1.74	.099	1.79	1.00 to 2.56	.759	.458	.781	.226 to 1.31
Pseudoword RT	1.73 (.335)	.997*	1.24	-2.13	.048	-2.20	-3.08 to -1.29	-1.42	.174	-1.45	-2.13 to -.754

RT: response time in seconds. BS1: Backward speaker 1; BS2: Backward speaker 2. Statistical comparison were performed via Crawford's two-tailed t-tests (Crawford & Howell, 1998; Crawford, Garthwaite, & Porter, 2010). The asterisks (\*) indicate significant differences at  $p < .05$ .



**Table S6.** VBM results for Backward speaker 1.

Cluster size	Peak MNI coordinates			Hemisphere	Anatomical label ( <i>n</i> of voxels)	Peak <i>t</i>
	<i>x</i>	<i>y</i>	<i>z</i>			
<b>61</b>	-34.5	-40.5	-7.5	Left	Parahippocampal (45) Fusiform (12)	4.93

**Table S7.** VBM results for Backward speaker 2.

Cluster size	Peak MNI coordinates			Hemisphere	Anatomical label ( <i>n</i> of voxels)	Peak <i>t</i>
	<i>x</i>	<i>y</i>	<i>z</i>			
<b>613</b>	48	33	12	Right	Inferior frontal (495) Middle frontal (113)	15.9
<b>372</b>	-37.5	46.5	13.5	Left	Middle frontal (332) Inferior frontal (40)	9.07
<b>60</b>	9	-87	19.5	Right	Cuneus (60)	5.07
<b>51</b>	-33	36	43.5	Left	Middle frontal (48)	4.85
<b>299</b>	4.5	-54	66	Right	Precuneus (220)	7.22
<b>72</b>	39	-45	63	Right	Postcentral (53) Superior parietal (19)	5.18

**Table S8.** Significant nodes of mean diffusivity (MD) that significantly differed between backward speaker 1 (BS 1) and the control group. Only results that survived both the Bonferroni corrected *p* threshold at the node level ( $p < .00416$ ) and the cluster correction (cluster > 5 contiguous significant nodes) are reported. Means (*M*) and standard deviations (*SD*) are reported for the control group. AF: arcuate fasciculus.

Significant results at $p \leq .00416$							
Controls							
Hemisphere	Tract	Node	<i>M</i>	<i>SD</i>	<i>BS 1</i>	<i>t</i>	<i>p</i> (2-tailed)
Left	Posterior AF segment	95	.76	.036	.89	3.47	.0029
		96	.76	.034	.90	3.96	.001
		97	.76	.033	.91	4.26	.0005
		98	.76	.033	.91	4.37	.0004
		99	.77	.033	.91	4.44	.0004
		100	.77	.032	.91	4.5	.0003
Right	Posterior AF segment	1	.75	.178	.88	4.1	.001
		2	.75	.178	.88	4.36	.000
		3	.74	.178	.89	4.52	.000
		4	.74	.178	.88	4.63	.000
		5	.74	.177	.88	4.56	.000
		6	.74	.176	.86	4.27	.001
		7	.74	.175	.84	3.85	.001
		8	.73	.175	.83	3.31	.004

**Table S9.** Significant nodes of mean diffusivity (MD) that significantly differed between backward speaker 2 (BS 2) and the control group. Only results that survived both the Bonferroni corrected p threshold at the node level ( $p < .00416$ ) and the cluster correction (cluster > 5 contiguous significant nodes) are reported. Means (M) and standard deviations (SD) are reported for the control group. AF: arcuate fasciculus.

Significant results at $p \leq .00416$							
Hemisphere	Tract	Node	Controls		BS 2	<i>t</i>	<i>P</i> (2-tailed)
			<i>M</i>	<i>SD</i>			
Left	Posterior AF segment	32	.74	.034	.86	3.42	.0033
		33	.74	.035	.87	3.56	.0024
		34	.74	.035	.88	3.72	.0017
		35	.74	.035	.88	3.89	.0012
		36	.74	.035	.88	4.01	.0009
		37	.74	.035	.89	4.05	.0008
		38	.74	.037	.89	3.99	.0009
		39	.74	.038	.89	3.89	.0012
		40	.74	.039	.89	3.80	.0014
		41	.74	.040	.89	3.73	.0017
		42	.74	.041	.89	3.68	.0019
		43	.74	.041	.89	3.61	.0022
		44	.74	.041	.89	3.53	.0025
		45	.74	.042	.89	3.45	.0030
		46	.74	.042	.89	3.38	.0036
		47	.74	.042	.88	3.32	.004
		Right	Uncinate fasciculus	85	.73	.04	.87
86	.73			.041	.89	3.67	.0019
87	.73			.041	.90	3.87	.0012
88	.73			.041	.91	4.06	.0008
89	.73			.041	.91	4.24	.0006
90	.73			.04	.91	4.33	.0005
91	.73			.04	.91	4.32	.0005
92	.74			.039	.90	4.2	.0006
93	.74			.039	.89	4.01	.0009
94	.74	.036	.88	3.81	.0014		
95	.74	.034	.87	3.56	.0024		

**Table S10.** Seed-to-voxel functional connectivity results based on resting-state data from Backward speaker 1.

Seed location (coordinates)	Clusters MNI coordinates			Cluster size	Hemispher e	Anatomical label	Minimum cluster size <i>FDR</i> - corrected [ $t(13) = 4.22$ ]
	<i>x</i>	<i>y</i>	<i>z</i>				
Left inferior frontal gyrus (pars triangularis) -50 29 9	54	-2	8	461	Right	(Pre)central operculum	262
	58	-60	-10	369	Right	Insula Heschl's gyrus Lateral occipital	
	58	-30	26	262	Right	Inferior temporal Middle temporal Parietal operculum Supramarginal Postcentral	
Right inferior frontal gyrus (pars triangularis) 52 28 8	-20	-52	62	372	Left	Lateral occipital Superior parietal	166
	50	-54	-2	342	Right	Inferior temporal Middle temporal	
	-60	-24	44	313	Left	Postcentral Supramarginal	
	0	20	28	302	Right/left	Anterior Cingulate	
	8	-54	64	246	Right	Superior parietal	
	-26	50	-12	238	Left	Frontal pole	
	32	60	-4	228	Right	Frontal pole	
	-6	-72	38	173	Right/left	Precuneus Postcentral Supramarginal	
38	-36	52	166	Right			
Left insular cortex -37 2 1	58	-62	-10	501	Right	Inferior temporal	118
	18	-98	10	411	Right	Occipital pole	
	-12	-102	-10	344	Left	Occipital pole	
	34	64	06	182	Right	Frontal pole	
	52	2	50	173	Right	Precentral gyrus	
	38	44	38	171	Right	Middle frontal gyrus	
	38	-34	40	153	Right	Postcentral	
	32	-84	-20	131	Right	Occipital Fusiform	
	14	-70	36	121	Right	Precuneus	
28	-48	68	118	Right	Superior parietal		
Right insular cortex 38 3 -1	58	-60	-12	688	Right	Inferior temporal	201
	-38	46	-18	507	Left	Frontal pole	
	32	-88	-20	376	Right	Cerebellum Cru1	
	44	48	-8	302	Right	Frontal pole	
	-24	52	-6	213	Left	Frontal pole	
-26	-92	-16	201	Left	Occipital pole		
Right supramarginal gyrus 62 -35 32	-10	-72	28	883	Right/Left	Cuneus Precuneus	147
	-30	56	-6	549	Left	Frontal pole	
	26	58	-6	471	Right	Frontal pole	
	36	34	46	365	Right	Middle frontal	
	-36	32	40	305	Left	Middle frontal	
	26	-50	68	153	Right	Superior parietal	
-54	26	16	147	Left	Inferior frontal		

**Table S11.** Seed-to-voxel functional connectivity results based on resting-state data from Backward speaker 2.

Seed anatomical label (coordinates)	Contrast	Clusters MNI coordinates			Cluster size	Hemisphere	Anatomical label	Minimum cluster size <i>FDR</i> -corrected [ $t(13) = 4.22$ ]
		<i>x</i>	<i>y</i>	<i>z</i>				
Left insular cortex -37 2 1	+	38	-92	-12	2567	Right/Left	Occipital pole	188
							Lateral occipital	
							Cuneus	
		-62	-20	4	188	Right Right Left	Inferior temporal Fusiform Posterior Superior temporal	
	-	-38	-50	-56	223	Left	Cerebellum	188
Right insular cortex 38 3 -1	+	-2	-72	18	810	Right/Left	Cuneus	165
		38	-84	-6	165	Right	Lateral occipital	
Left supramarginal gyrus -60 -39 31	+	-30	-98	-6	182	Left	Occipital pole	182

**Study 5.** *Are verbal repetition deficits over-represented in males? A systematic literature review on post-stroke aphasia<sup>5</sup>*

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<sup>5</sup> This article corresponds to:

Torres-Prioris, M. J., Pertierra, L., López-Barroso, D., Dávila, G., Berthier, M. L. Are verbal repetition deficits over-represented in males? A systematic literature review on post-stroke aphasia. Working article.



# Are verbal repetition deficits over-represented in males? A systematic literature review on post-stroke aphasia

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## **Abstract**

### **Background**

Repetition is an essential function for language acquisition in childhood, new word learning during adulthood, and a major resource in aphasia rehabilitation such as Imitation-Based Aphasia Therapies. Imitation and repetition of verbal information in humans is a complex function requiring the concerted action of large-scale neurocognitive networks, which may have individual and sex-related differences in their functional organization and configuration. However, until now there are no studies aimed to explore sex differences in repetition abilities after stroke.

### **Methods & procedure**

In the present study we conducted a systematic literature review devised to examine sex differences in verbal repetition prevalence in post-stroke aphasia. We examined the prevalence of two aphasia subtypes, conduction (CA) and transcortical (TA), which were selected as index language disturbances based on their impaired and preserved repetition abilities, respectively. The male:female ratio was compared with the expected by stroke prevalence.

### **Outcomes & results**

The review disclosed that the proportion of male in the CA group was higher than expected, whereas the expected was found in the TA. These outcomes suggest that males may be more vulnerable than females to suffer from stroke-related aphasias with enduring repetition deficits. Although, the present work is not exempt from limitation, it seeks to encourage further studies that explore sex ratio among patients with verbal repetition deficits. Hence, future studies may consider not only sex as a relevant factor in the clinical profile of post-stroke aphasia, but could address the neural correlates of sex-related brain differences in the prevalence of CA.

**Keywords:** Language repetition, conduction aphasia, sex dimorphism, arcuate fasciculus.



## Introduction

Imitation and repetition of verbal material are key functions in the acquisition and development of language and these skills may contribute to overcome language deficits in aphasia, a condition broadly defined as the partial or total loss of language functions after acquired brain damage. In the past decades, the generically termed “Imitation-Based Aphasia Therapies” (Duncan & Small, 2016; Lee et al., 2010) have emerged as an important milestone in the treatment of aphasia. These therapies are aimed to increase language production through verbal imitation and repetition, based on the evidence of shared neural mechanisms for speech perception/observation and the execution of verbal acts (Duncan & Small, 2017). In persons with aphasia (PWA), improvements in verbal production are associated to compensatory activity in cortical and white matter tracts in the spared left hemisphere regions as well as in the intact right hemisphere (Santhanam, Duncan, & Small, 2018; Sarasso et al., 2014).

Verbal repetition is a complex function requiring the concerted action of large-scale neurocognitive networks that involves both left and right perisylvian areas (Hope et al., 2014; Mesulam, 1990; Saur et al., 2008). Mechanistically, speech repetition requires the translation of the phonological code into the motor code, which will eventually allow its articulation (auditory-motor integration) (Hickok & Poeppel, 2007). Some authors suggest that auditory-motor integration of speech in both healthy subjects (Hickok et al., 2011) and PWA (Rogalsky et al., 2015) requires the activity of the left sylvian parieto-temporal (Spt) area, whereas others point that the activity of the arcuate fasciculus (AF) is key for this process (Lopez-Barroso et al., 2013b; Parker Jones et al., 2014; Saur et al., 2008; Schulze, Vargha-Khadem, & Mishkin, 2012). Importantly, anatomical and functional differences in brain structures involved in auditory-verbal repetition seem to be linked to differences in verbal tasks performance. For instance, López-Barroso and colleagues reported that better ability to remember new learned words correlated with greater white matter integrity of the left AF (Lopez-Barroso et al., 2013) and increased functional connectivity within the auditory-motor network (López-Barroso et al., 2015). In this line, Catani and colleagues (2007) reported that better performance in a verbal recall task (California Verbal Learning Test) (Delis, Kramer, Kaplan, & Ober, 1987) was associated with a well-developed long segment of the AF in both hemispheres (i.e., bilateral pattern) (Catani et al., 2007). Berthier and coworkers described two cases showing similar lesion distribution and volume in the left hemisphere but different verbal repetition capacity (Berthier et al., 2013). The dissociated repetition performance in such cases could be explained by dimorphic development of the right long segment of the AF, being well developed in a female with preserved repetition and inexistent in a male with

repetition deficits (Berthier et al., 2013). Additionally, a study exploring predictive anatomical biomarkers of spontaneous recovery in PWA showed that the presence of a well-developed long segment of the AF in the right hemisphere favor language recovery after left perisylvian damage (Forkel et al., 2014). Altogether, these results suggest that premorbid organization of language-related pathways (e.g. AF), which are subjected to inter-individual variability and sex differences (Catani et al., 2007; Lopez-Barroso et al., 2013; Madhavan, McQueeny, Howe, Shear, & Szaflarski, 2014; Thiebaut de Schotten et al., 2011), might influence the aphasia profile and, presumably, the response to behavioral interventions.

Among sex-related differences in brain structure, a recent meta-analysis identified that females have, on average, greater volume than males in areas of the right hemisphere homologues to the language areas of the left hemisphere (inferior frontal gyrus, pars triangularis, pars opercularis, planum temporale and Heschl's gyrus) (Ruigrok et al., 2014). In accordance, in the above-mentioned study, Catani and colleagues (Catani et al., 2007) found that on average females had greater development of the right AF, a tract connecting the superior temporal gyrus and the inferior frontal gyrus, thus having a more symmetrical pattern (~60%) than males (~15%) (see also (Thiebaut de Schotten et al., 2011), although this was not replicated in other study (Allendorfer et al., 2016). Further sex-related differences in structural and functional connectivity have been reported, indicating that females have greater inter-hemispheric connectivity, whereas males have greater intra-hemispheric connectivity (Ingalhalikar et al., 2014; Sun et al., 2015). Interestingly, these divergent patterns of connectivity seem to be linked to sex differences in cognitive performance (Satterthwaite et al., 2015).

Despite the described anatomo-functional sex-based brain differences and their relevance to cognitive functioning, until now there is no clear behavioral evidence on whether verbal repetition may have different sex preponderance among PWA, neither whether sex may influence the response to certain aphasia therapies. Generally, the aphasic literature has yielded mixed results regarding sex rate among PWA (Basso, Capitani, & Zanobio, 1982; Di Carlo et al., 2003; Engelter et al., 2006; Ferro & Madureira, 1997; Hier, Yoon, Mohr, Price, & Wolf, 1994; Kang et al., 2010; Kertesz & Benke, 1989; Renzi, Faglioni, & Ferrari, 1980; Scarpa, Colombo, Sorgato, & De Renzi, 1987) and, specially, there are not studies aimed to explore prevalence of auditory-verbal repetition deficits among females and males with aphasia. A very recent meta-analysis has found that aphasia is more frequent among females than males, with a rate ratio of 1.10-1.14, but these differences disappear when controlling by age (Wallentin, 2018). However, this finding is mainly based on sex ratio in the acute stage and may not reflect compensatory changes occurring during spontaneous recovery,

where premorbid brain anatomy may play an important role (Forkel et al., 2014). Further, although this study made a significant contribution in summarizing the existent evidence in aphasia rates among females and males, is not informative on sex distribution in the different aphasia types and symptoms.

The aim of our study was to analyze the relationship between sex and one specific type of post-stroke aphasia, *conduction aphasia* (CA), a language disorder chiefly characterized by repetition deficits. For this, we performed a systematic review of the existing studies reporting cases of CA. Additionally, two other types of aphasias (i.e., transcortical aphasias - TA) showing a different clinical profile to CA, that is preserved repetition abilities, were also studied as a control group. Since verbal repetition is a crucial component of language (re)learning and a target domain in language therapies such as Imitation-Based Aphasia Therapies (see reviews in Duncan & Small, 2016; Eom & Sung, 2016; Salis et al., 2015), we envisage that exploring sex differences in CA may contribute to gain further knowledge on the role of demographic factors in the clinical diagnosis and treatment of PWA. Based on the abovementioned sex-related brain dimorphisms, namely greater volume of the right AF, greater volume in perisylvian areas of the right hemisphere and greater interhemispheric connectivity for females than males, it is plausible that brain configuration in females is more suitable to compensate repetition deficits after damage in the left hemisphere via recruitment of the right hemisphere than males. Thereby, we hypothesize that aphasic males are more likely to show enduring repetition deficits than aphasic females, thus CA would be more frequently observed in males than in females. Although our study was based on clinical data and could not address the role of sex-related brain differences in the prevalence of CA, the hypothesis that we pose here are based on the available evidence regarding sex differences in brain structure and functioning.

## Methods

### Population target of this study

In this study, the syndrome of CA was chosen as a target post-stroke language impairment for the following reasons: (i) the core clinical feature of CA is a deficit in verbal repetition; (ii) overall, CA has an identifiable anatomical correlate, that is the simultaneous involvement of the left long AF segment and its overlying cortical mantle (i.e., temporo-parietal and frontal regions) (Berthier et al., 2012; Rogalsky et al., 2015) (but see Bernal & Ardila, 2009), and (iii) the AF and the overlying cortical regions are possibly sexually dimorphic (Catani et al., 2007; Ruigrok et al., 2014).

As a control disorder, we reviewed other types of post-stroke aphasia profiles known as TA, which are paradigmatically characterized by preserved verbal repetition in the face of (i) non-fluent speech and good auditory comprehension (transcortical motor aphasia - TCMA); and (ii) fluent speech and poor auditory comprehension (transcortical sensory aphasia - TCSA). Transcortical aphasics were selected due to two main reasons. On the one hand, this group is composed of subjects with an aphasic profile that does not overlap in their surface symptoms and clinical course with CA. In other words, TA would not evolve from or into CA, and therefore such cases constitute an independent sample of post-stroke aphasics. On the other hand, causative lesions of TCMA and TCSA would reasonably be expected to affect different cerebral structures (i.e., lesions that spare the perisylvian language area) than those causing CA. Cases of mixed transcortical aphasia (MTCA) were not reviewed because these subjects show a severe language impairment with low performance in every language task and repetition sometimes is far from being relatively spared as occur in TCMA and TCSA (MTCA scores ranged from 5 to 10 in the repetition subtest of the Western Aphasia Battery (WAB) (Kertesz, 1979). Thus, we consider a group composed of cases with TCMA and TCSA as the most accurate control group for CA, as diagnostic criteria for these two aphasic syndromes requires good repetition (scores ranged from 8 to 10 in WAB's repetition subtest – Kertesz, 1979)

### **Search Strategy**

A systematic review according to PRISMA standards (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) was conducted. Search terms used in the algorithm included “conduction aphasia”, “associative aphasia”, “afferent motor aphasia” and “central aphasia”. The search was run in two computerized databases, Medline (PubMed) and PsycINFO, in order to retrieve all reported cases of CA from the literature until November 2018. An additional search was done for the control TA group, comprising the same period of time and using an analog algorithm, which included the terms “transcortical aphasia”, “transcortical motor aphasia”, “transcortical sensory aphasia”, “Gogi aphasia”, “anterior isolation syndrome” and “posterior isolation of the speech area”. References of retrieved articles were thoroughly screened for further relevant articles, letters, book chapters and meeting abstracts. Only English-written publications were reviewed.

### **Data Extraction and Quality Assessment**

Two of the authors (MJTP and LP) reviewed the title and abstract of each retrieved publication, and thereafter the full text was assessed for eligibility. Disagreements were resolved by consultation with one of the senior authors (MLB) with experience in diagnosing

these aphasic syndromes. Aphasic subjects considered by the respective publication's authors to suffer from CA or TA (TCMA or TCSA) by means of formal standardized testing or reliable clinical bedside assessment were included in the analysis. Articles providing no clear link between sex and aphasia type were not included. Only articles that had available sex information for each individual PWA, or for each type of aphasia were included. The following inclusion criteria were used: first single unilateral stroke (ischemic or hemorrhagic);  $\geq 18$  years of age; no prior history of developmental disorders, no concomitant neurological or psychiatric disease, substance abuse or severe head trauma, nor any other general medical condition that could affect cognitive performance. Information sought included subject's sex and, when available, handedness, education level, time post onset and severity of aphasia, treatment received and lesion localization, assessed by neuroimaging and/or autopsy reports.

### **Statistical analysis**

First, a chi-squared test of independence was performed to determine whether sex and aphasia type were associated. Secondly, in order to further explore the reviewed data, and to take into account the greater prevalence of stroke among males, the male proportion in both CA and TA groups calculated from our database was compared with the male proportion in the stroke population calculated from male:female ratio. The male:female ratio was obtained from a systematic review on stroke prevalence (Appelros, Stegmayr, & Terent, 2009). The age adjusted male:female pooled ratio calculated from 13 different prevalence studies was 1.41 (95% CI, 1.12 to 1.59), meaning that male would account for 58.51% of chronic stroke patients (Appelros et al., 2009). Thus, the male prevalence in CA and TA groups obtained from our database were compared to the male prevalence in stroke patients using a binomial test. The original aim was to compare the male proportion found in the CA and TA groups with the male prevalence in chronic post-stroke aphasia. Higher proportion of males is usually found in the aphasic population due to the higher incidence of stroke among them, however ambiguous results have been reported in the last decades regarding this matter (Kertesz & Sheppard, 1981; McGlone, 1977; Renzi et al., 1980; Scarpa et al., 1987) preventing us from using this as reference value. The most reliable data on this issue comes from the recently published meta-analysis (Wallentin, 2018). In the mentioned study, the reported female:male ratio of 1.10 – 1.14 was calculated dividing the percentage of females with aphasia from the total of female with stroke by the percentage of males with aphasia from the total of males with stroke. Nevertheless, since Wallentin's study (Wallentin, 2018) do not report enough information about the sex distribution in the stroke group, and since the studies included report mainly data from the acute stage while our data includes mainly

chronic cases (> 6 months), we considered that comparing the percentage of male found in the CA and in TA samples with the proportion of males in the stroke population was the more accurate procedure. In fact, this alternative parameter was proposed by Basso and colleagues (Basso, Forbes, & Boller, 2013) as a reference to compare the prevalence of post-stroke aphasia.

All reported cases collected from the literature were included. However, with the aim of controlling from potential biases, an additional analysis of a subsample was carried out to exclude case-series and group studies reporting only males or females. This exclusion criterion was applied over the total cases of aphasia reported, not only on the CA or TA groups. For example, Haley, Jacks, and Cunningham's study (Haley, Jacks, & Cunningham, 2013) reported 5 cases of males with CA and none female. However, the total aphasic sample of this study, including other type of aphasias, was of 19 males and 13 females. Thus, since the overall sample included both sexes and no bias were expected, data coming from this study was included in this additional analysis. Note that data coming from Veterans Hospitals reporting only males was excluded in this additional analysis. Single cases were included after checking that no significant difference were seen between the ratio of male:female found in our database and the male:female ratio expected from stroke prevalence.

All statistical analyses were performed with SPSS software, version 25 (IBM, Armonk, NY, USA).

## Results

A total of 1.201 items were screened, with marked predominance of full text articles. Publications included consisted mainly of single case reports, case-series, case-control studies, cohort studies, as well as clinical trials for pharmacological or aphasia therapy interventions, which included CA and TA among other types of aphasia. Figure 1 depicts the flow of information through the different phases of the systematic review. There were no articles aimed to investigate the prevalence of CA or TA or sex susceptibility in the profile of aphasia. Publications covered from 1947 to 2018, but cases published before these dates were also included, although their original references are not listed. For instance, these included the original description of CA by Osborne in 1834 (Breathnach, 2011) and Lichtheim's case of Samuel Berger in 1885 (Köhler, Bartels, Herrmann, Dittmann, & Wallesch, 1998).

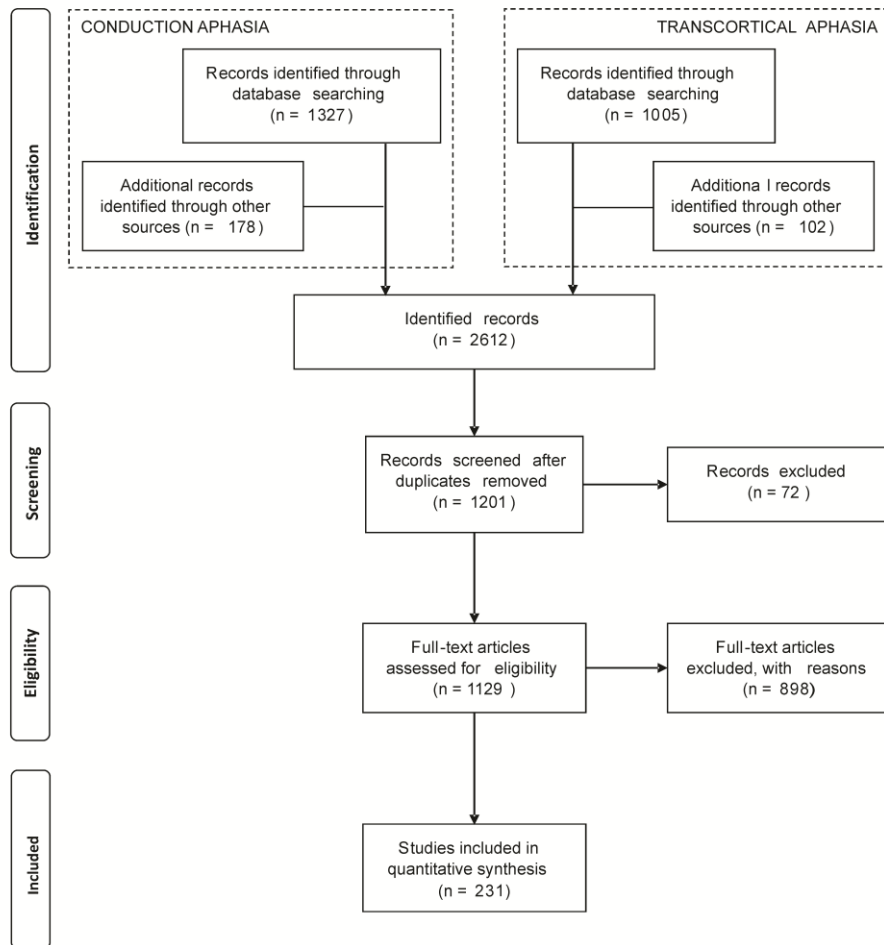


Figure 1. Flow chart of the different phases of the systematic review based on PRISMA statement ([www.prisma-statement.org](http://www.prisma-statement.org)).

Two hundred and thirty-one publications were selected from the literature search, accounting for a total of 764 cases finally included in the database. Among those, there were 506 (66.2%) subjects with CA extracted from 159 studies, and 258 (33.8%) subjects with TA (TCMA and TCSA) extracted from 104 studies. Note that 32 studies reported cases of both CA and TA. In the CA sample (n = 506), there were 376 (74.3%) males and 130 (26.7%) females. In the TA sample (n = 258), there were 161 (62.4%) males and 97 (37.6%) females. Thus, the ratio of CA:TA in the male group was of 2.33 and for the female group was 1.34. The TA group consisted of 123 (47.7%) subjects with TCMA, 112 (43.4%) with TCSA and 23 (8.9%) generally classified as having TA with no further subtype classification. In the CA group, only 18 (3.5%) subjects were further classified as having reproduction CA (n = 6; 1.2%) and repetition CA (n = 12; 2.4%) subtypes, whereas the remaining cases were generally classified as CA. Reproduction conduction aphasia (CA) is characterized by phonemic

**Table 1.** Summary of sociodemographic and clinical information of PWA included in the study.

	CA		TA	
	Male [n=376; 74.3%]	Female [n=130; 25.7%]	Male [n=161; 62.4%]	Female [n=97; 37.6%]
Age, years (SD) [n]*	58.11 (13.47) [274]	59.05 (14.73) [108]	58.42 (12.41) [133]	63.66 (11.86) [76]
Years of Education (SD) [n]*	13.10 (3.18) [107]	12.55 (3.15) [51]	12.43 (4.14) [53]	12.19 (3.21) [32]
Handedness [n]*	RH [229]; LH [13]; AH [1]	RH [81]; LH [2]; AH [1]	RH [91]; LH [3]; AH [0]	RH [56]; LH [1]; AH [0]
TPO [n]*	< 6 [76]; ≥ 6 [159]	< 6 [36]; ≥ 6 [66]	< 6 [27]; ≥ 6 [56]	< 6 [23]; ≥ 6 [29]

Note that only studies for which this information was available are included. \*n: indicates number of cases for which the information was available; RH: right handed; LH: left handed; AH: ambidextrous; TPO: Time post-onset indicated in month.

paraphasias in all verbal domains and recurrent production of sequential phonemic approximations to the target word aimed to self-repair errors (conduite d'approche) (Nadeau, 2001; Tim Shallice & Warrington, 1977). Repetition CA shows virtually isolated repetition deficits, which have been attributed to a selective impairment in auditory-verbal short-term memory (Nadeau, 2001; Tim Shallice & Warrington, 1977).

The additional analysis in which case-series and groups studies that reported only males or females were excluded was comprised of a total of 189 studies (101 reporting cases of CA, 58 reporting cases of TA and 30 reporting both), accounting for 599 PWA (63.8% males; 36.2% females). Among those, there were 373 cases of CA, composed of 247 (66.2%) males and 126 (33.8%) females. There were 226 cases of TA, composed of 135 (59.7%) males and 91 (40.3%) females. In this case, the ratio of CA:TA in the male group was of 1.82 and for the female group was 1.38. Table 1 depicts sociodemographic and clinical characteristics of PWA included in the present study, when available.

Chi-squared test of independence (Yates' corrected) indicated a significant association between sex and aphasia type when considering the whole sample ( $\chi^2(1) = 11.03$ ,  $p = .001$ ) but not when the subsample was

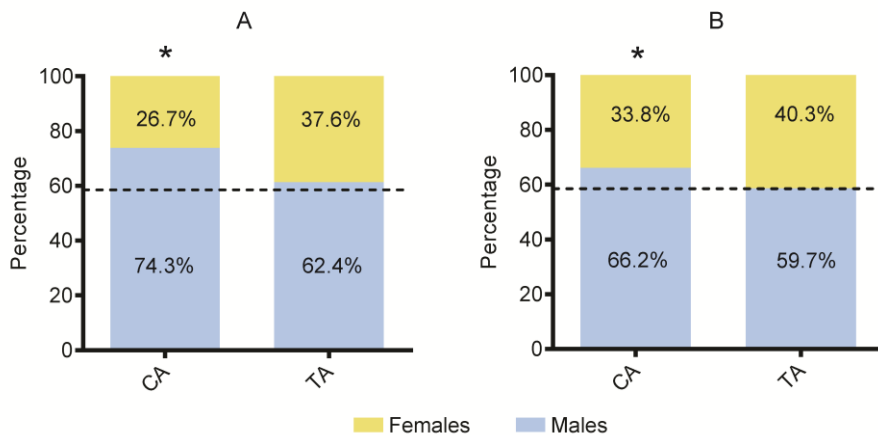
analyzed ( $\chi^2(1) = 2.56$ ,  $p = .130$ ). However, note that the expected probability calculated here with the chi-square test does not consider sex differences in stroke prevalence.

Considering the whole sample, results from the binomial test indicated that the proportion of males in the CA group (i.e., 74.3%) was significantly higher than the expected



58.51% by stroke prevalence ( $p < .001$ ; one-sided; 95% CI, 70.3 % to 78.1%). Conversely, no significant differences were observed between the proportion of males in the TA group (i.e., 62.4%) and the expected by stroke prevalence ( $p = .114$ ; one-sided; 95% CI, 56.2% to 68.3%). Since we are operation with proportion, necessarily the opposite pattern is found for females in the CA group (i.e., 26.7%), meaning a lower proportion of females in the CA group than expected by stroke prevalence, and no significant differences between the proportion of females in the TA group (i.e., 37.6%) and the expected by stroke prevalence. These results remained unchanged in the additional analysis in which group studies that reported only males or females were excluded. In this case, the binomial test indicated that the proportion of 66.2% of males with CA was higher than the expected 58.51% ( $p = .001$ ; one-sided; 95% CI, 61.2% to 71%). For the TA group, the additional analysis showed that the observed proportion of males (i.e., 59.7%) did not differ from the expected by stroke prevalence ( $p = .380$ ; one-sided; 95% CI, 53% to 66.2%).

A further analysis comparing the proportion of males found in the CA group (i.e., 74.3%) with the proportion found in the TA (i.e., 62.4), indicated that the proportion of males was significantly higher in the CA group ( $p < .001$ ; one-sided; 95% CI, 70.3 % to 78.1%). Similar results were found in the additional analysis of the subsample, indicating that the 66.2% found in the CA group was significantly higher than the 59.7% found in the TA group ( $p < .006$ ; one-sided; 95% CI, 61.2% to 71%).



**Figure 2.** Depicts the proportion of males and females in the target CA group and in the control TA group when considering the whole sample (A), and when case-series and group studies reporting only males or females were excluded (B). The dotted line represents the proportion of males expected by stroke prevalence according to Appelros et al., 2009. The asterisks indicate significant differences ( $p < .05$ ) between the proportion of males found in our data set and the proportion of males expected by stroke prevalence.

## Discussion

In the present study we conducted a systematic literature review of published cases of CA and TA with the aim of exploring whether sex differences in the rate of repetition deficits after stroke exist. Our findings reveal a higher proportion of males in the group of aphasia characterized by repetition deficits (i.e., CA) than in the group with preserved repetition (i.e., TA), being this proportion greater than the expected from the proportion of males in the general stroke population (58.51%). Conversely, the proportion of females in the CA was lower than expected by stroke prevalence. In other words, our results provide clinical data of greater prevalence of auditory-verbal repetition deficits among post-stroke males compared to females. By contrast, the proportion of males in the control group (i.e., TA group) did not differ from the expected by general stroke prevalence in males. Recently, Wallentin's study (Wallentin, 2018), reported no differences in aphasia rate, but this study did not provide information about putative differences in aphasic symptoms such as repetition deficits. Thus, our cross-sectional study adds important data on the status of impaired auditory-verbal repetition domain, a typical feature of CA complementing previous studies on aphasia rate among sex. Importantly, the present study was guided by a hypothesis based on the current evidence on sex differences in brain anatomy and functioning pointing that females have a more tuned right neural network that might play a role in the recovery from verbal repetition abilities.

Repetition impairment is a constant feature of perisylvian aphasic syndromes (Albert, Goodglass, Helm, Rubens, & Alexander, 1981; Berthier, 2005). Further, verbal repetition is a key component of phonological working memory (rehearsal mechanism), essential for language acquisition during childhood and word learning in adulthood (López-Barroso et al., 2011). Thus, emerging model-based aphasia therapies incorporate audio and audiovisual repetition-imitation training as a major resource for promoting language recovery (Berthier, Dávila, Green-Heredia, et al., 2014; Eom & Sung, 2016; Fridriksson et al., 2012; Salis et al., 2015). Since repetition abilities have a pivotal role in language re-learning and therapy during post-stroke aphasia recovery, the assessment of sex vulnerability to develop long-lasting repetition deficits and its recovery possibilities may be of utmost importance.

Although the neuroanatomical correlates of CA and TA reviewed herein could not be reliably examined, we suggest that one likely source of the different prevalence of sex in CA is based on sex-related brain dimorphisms. It is possible that females, by virtue of having higher interhemispheric connectivity (Gur & Gur, 2017; Ingallhalikar et al., 2014; Sun et al., 2015) and greater volume of gray and white matter on areas of the right hemisphere homologues to the areas involved in verbal repetition in the left hemisphere compared to

males (Catani et al., 2007; Ruigrok et al., 2014), are more apt than males for verbal repetition, especially after brain damage. Such a biological endowment may assist in the recruitment of the right hemisphere (Berthier et al., 2013; Forkel et al., 2014) after damage to the language areas in the dominant hemisphere. We believe that sex differences in verbal repetition become more apparent in brain-damaged than in healthy subjects. Healthy literate subjects perform at ceiling while repeating single words, words lists, and sentences, making difficult to identify errors (see data in (Berthier, 2001; Castro-Caldas, Petersson, Reis, Stone-Elander, & Ingvar, 1998; Rosselli, Ardila, & Rosas, 1990) presumably because the activity of the left hemisphere prevails and it is enough to sustain a flawless execution. And yet, sex differences in healthy subjects may appear in more demanding word learning tasks through verbal repetition with females outperforming males (Catani et al., 2007) and after brain damage (Berthier et al., 2013; Forkel et al., 2014). In this regard, preliminary data show that the architecture of the non-lesioned right AF might be a biological marker to predict the natural evolution of repetition deficits in PWA (see Forkel et al., 2014). However, further studies in large sample sizes are needed to unveil whether females have a more bilateral pattern of the direct segment of the AF and whether a strong left lateralization of the AF might be an anatomical predictor of persistent verbal repetition deficits as occur in CA. Thus, longitudinal studies are needed to address this issue.

The present systematic literature review should be interpreted in light of some methodological limitations. One limitation is the existing differences between the reviewed studies as the goals, available information, and scope varied from one reviewed article to another. Some demographic and clinical variables could not be adequately controlled. Unfortunately, we do not have reliable information regarding lesion volume and localization in most cases, thus overlooking the role of lesion characteristics. Additionally, we must note that only in approximately two thirds of the reviewed cases, data on time post-onset of aphasia was available. As time of evolution of stroke itself may influence aphasia clinical subtype, we recognize this as a possible bias when trying to assess its association to sex. However, chronic aphasics accounted for 66% of subjects in all subgroups. Finally, publication bias is another major concern of any systematic review of published cases. However, being CA a relatively infrequent aphasia syndrome, there seems to be no statistical alternative in order to ascertain sex relative prevalence.

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# CHAPTER 4



## Chapter 4. General conclusions

Before jumping to the general conclusions of this dissertation, I address some limitations that need to be acknowledged, and point out possible directions for future studies.

### Limitations and future directions

First, the studies included involved small sample sizes. However, single case studies have been foundational in the development of neuropsychology (Laine & Martin, 2012), and, although they do not have the confirmatory power of large studies, they serve as hypothesis generators and, at the same time, allow exploring individual differences frequently overlooked in group studies.

*Study 1* provides an interpretation of *Conduite d'approche* and mitigated echolalia as symptoms that emerge from compensatory attempts and proposes putative alternative pathways supporting these behaviors. However, larger studies adopting lesion-approaches (e.g., VLSM) to correlate lesion location with these behaviors are needed to bring further evidence on this issue. In addition, longitudinal studies are needed to provide evidence on the emergence and evolution of these behaviors across time. Further, *Study 2* and *Study 3* suggest that echolalia may be a compensatory behavior aimed to overcome some linguistic (i.e., comprehension) and short-term memory deficits. Yet, further larger studies are needed to determine whether this repetitive behavior is useful to improve comprehension or other linguistic functions, and under which circumstances (i.e., cognitive, neural). This will have clinical relevance informing therapeutic decisions.

Lastly, this dissertation explores sources of variability in verbal repetition and found sex to be a relevant variable. Specifically pointing out lower prevalence of repetition deficits among women. In this regard, although we provide speculative explanations for this finding, we could not directly address the origin of this difference. Yet, given the low prevalence of TAs this was the more putative approach to address the issue of sex differences in verbal repetition outcome after brain damage. Future studies are needed to: (1) replicate our findings; (2) determine whether this pattern of lower repetition deficits among women is already present at the acute stage or, alternatively, emerges afterwards; (3) provide evidence on differences in compensatory brain changes (or pre-existing differences) explaining verbal repetition outcomes in females and males after brain damage.

## Conclusions

The present dissertation includes five studies that address different aspects of verbal repetition in persons with chronic aphasia as well as in a model of phonological expertise in healthy persons named backward speech. The results of these studies lead to relevant conclusions described below.

### Block 1

*Study 1.* Results from this study suggested that the symptoms of *conduite d'approche* and mitigated echolalia reflect compensatory changes within the preserved stream in the left hemisphere and alternative right hemisphere pathways that emerge when the main pathway for a given function is damaged. Thus, echolalia seems to emerge from a spared left dorsal stream when the ventral stream is damaged. Likely, the symptom of *conduite d'approche* results from the activity of the ventral stream when the left dorsal stream is out of functioning. Although at present, these repetitive verbal behaviors only provide suboptimal performance in persons with aphasia, the novel interpretation of these behaviors as active attempts to overcome a language deficit, open new avenues for remodeling the language network with modern interventions (e.g., non-invasive brain stimulation, drugs) to promote recovery.

*Study 2.* This opinion article analyzed different types of echolalia which may lay in a continuum of severity, suggesting that it represents a heterogeneous symptom of aphasia. Thus, exploring the effects and the global interference that echolalia has in communication at individual level is crucial to enrich its clinical management. Further, recommendations regarding its assessment and treatment were provided.

*Study 3.* The results from this single case study suggested that mitigated echolalia interfering with functional communication may be modulated through treatment. Further, it is shown that in the studied subject, mitigated echolalia emerged mainly as a strategy to compensate for comprehension and short-term memory impairments associated to a large temporal lesion. Functional and structural neuroimaging analysis suggested that ME may emerge from the activity of remnants of the left dorsal stream and homotopic perisylvian counterpart in the right hemisphere.

### Block 2

*Study 4.* Results from this study suggested that expertise in backward speech in healthy subjects, which relies on sequencing processes of phonological encoding, induces functional and structural adaptations mainly within the optimized route for phonological processing (i.e., dorsal stream) and limited involvement of the ventral stream. Further,

functional imaging results suggested that backward speakers feature greater synchrony between language-related regions and areas involved in high-level visual and domain-general processes (e.g., attention), which may reflect and implicit visualization of the to-be-reversed strings as well as the increment of cognitive demands placed by reversal processes. Yet, great individual differences in the neural features of each subject were observed, which we speculate to be related to the strategy used during backward speech, depending more on phonological memory in one case and in visualization strategies in the other.

**Study 5.** Results from this study provide evidence of different ratios of repetition deficits in males and females after stroke, with the formers showing greater prevalence than the latest. One putative explanation of this finding is that the described anatomical differences depicting greater volume in right cortical areas and relevant white matter tracts (i.e., AF) homotopic to the ones involved in verbal repetition in the left hemisphere, together with the greater inter-hemispheric connectivity, may favor recovery through recruitment of right areas in females. Importantly, this finding may encourage further investigations posing sex as a putative relevant variable.

Overall, the results of the 5 studies presented herein suggest that cognitive strategies and neural correlates involved in a given task change after brain damage, and that symptoms previously considered as “deleterious errors” may reflect attempts to overcome language deficits resulting from plastic changes within available tissue. Further, while recovery of language after brain damage seems to rely on remnant and alternative pathways when the major pathways are damaged, differences between expert backward speakers and controls suggest that plastic changes (or pre-existing differences) occur mainly within networks devoted to the task, and lesser over alternative ones. Yet, the increased cognitive demands placed by phoneme reordering leave traces in the brain circuitry in the form of greater functional connectivity between domain-general and phonological-related processing areas. Although further larger studies are certainly needed, together this leads us to think that the different components of the human language network are specialized and, when available, improvement of functions is supported by reshaping and tuning of these networks. Importantly, when the preferential pathway for a given task is not available, redundant connections and compensatory changes aid performance, although such performance might be suboptimal. Yet these alternative routes may be enhanced through different therapeutic interventions. Importantly, inter-individual differences in verbal repetition really exist. Thus, differences in the strategy used to comply with a task demand, the type and amount of behavioral training or the action of biological strategies (e.g. drugs) coupled with pre-existing brain differences may be a source of variability in the ability to repeat. Among this last one,

this dissertation points out sex as an important variable influencing outcomes in verbal repetition after brain damage.

I believe that the finding and the clinical suggestions provided in this dissertation will contribute to the understanding of the brain networks supporting the improvement of linguistic abilities and management of some common symptoms of aphasia. Thus, the results of this work may inform models of brain plasticity and aid clinical interventions.

# CHAPTER 5





## Chapter 5. Resumen (*en español*)

### Introducción

#### Perspectiva general de la repetición verbal en el presente trabajo

El lenguaje es la función cognitiva más compleja del cerebro humano. Nos permite crear un sinfín de posibles construcciones, sustentando nuestra capacidad de pensamiento abstracto y de comunicación. Entre las funciones que integran el lenguaje, la capacidad de repetición verbal parece ser la más simple. No obstante, esta función requiere la traducción de un código fonológico a un patrón motor (proceso conocido como integración audio-motora Hickok & Poeppel, 2007), lo cual recae en una serie de subprocesos. Así, repetir un estímulo (palabra, pseudopalabra o frase) de forma exitosa requiere procesar auditiva y fonológicamente el estímulo, cuando sea posible acceder al trazo de memoria asociado a dicho estímulo (en el caso de palabras conocidas), y mantener una correcta representación en la memoria a corto plazo hasta transformar el código fonológico en un patrón motor que será finalmente ejecutado. Este proceso se sustenta en una compleja red cerebral en la que participan regiones perceptivas, motoras y las conexiones entre ellas, en estrecha relación con otros procesos como el control inhibitorio y la memoria.

Repetir una secuencia fonológica en nuestra lengua suele ser una tarea fácil para la mayoría de nosotros, pero puede resultar más demandante si la secuencia de fonemas a repetir no tiene significado (p.ej., pseudopalabras), pertenece a otro idioma o es demasiado larga y, aún más, si requiere de manipulaciones intermedias como invertir el orden de las sílabas o fonemas que la componen. Sin embargo, existe variabilidad individual y la repetición de una sílaba puede ser extremadamente difícil para una persona con afasia, mientras que, por ejemplo, repetir estímulos invirtiendo el orden de los fonemas puede ser una tarea fácil para una persona con pericia en este proceso. Estas disparidades se pueden explicar por diferencias anatómicas y funcionales en la red cerebral que sustenta la capacidad de repetición y en sistemas relacionados. De hecho, diferencias en esta red han sido descritas como sustrato neuronal de algunos tipos de afasias, así como también de diversos tipos de pericia lingüística (p.ej., traductores simultáneos y fonetistas).

Aunque las técnicas modernas de neuroimagen han permitido establecer con bastante claridad la red cerebral que sustenta la función de repetición verbal en sujetos sanos, muchos aspectos de esta función lingüística han sido poco estudiados en personas con afasia y en modelos emergentes de pericia lingüística. Por lo tanto, el presente trabajo busca explorar las características cognitivas y los correlatos neuronales de la repetición verbal desde diferentes perspectivas, incluyendo modelos de repetición disfuncional (i.e., personas con

afasia) y modelos de pericia lingüística (i.e., habladores inversos), y con ello contribuir a mejorar el conocimiento de algunos síntomas clínicos (p.ej., ecolalia) caracterizados por repetición disfuncional, y las bases cerebrales asociadas. Los objetivos específicos de cada estudio incluido se abordan en un apartado posterior. Antes, se presentan los antecedentes que justifican dichos objetivos y la evidencia científica derivada de estudios previos en la que se sustentan los mismos.

### **Importancia de la repetición verbal**

Filogenéticamente, el desarrollo de la red cerebral que sustenta la capacidad de integración audio-motora —proceso clave que subyace la capacidad de repetición (y que constituye el bucle fonológico de memoria de trabajo)— apareció como una función clave que propició el desarrollo de un sistema lingüístico complejo (Aboitiz, 2018). Se ha propuesto que la optimización de este sistema ha permitido a nuestros ancestros aprender secuencias fonológicas de complejidad creciente por medio de la repetición e imitación (Aboitiz, 2018).

Asimismo, a nivel ontogenético, la repetición verbal y la imitación juegan un papel clave en la adquisición del lenguaje. Diversos estudios de adquisición de primera y segunda lengua en niños con desarrollo normal muestran que la adquisición de vocabulario está fuertemente relacionada con la capacidad para repetir secuencias fonológicas sin significado (i.e., pseudopalabras) (ver revisión en Baddeley et al., 1998). Así, la obtención de mejores puntuaciones en repetición de pseudopalabras se ha relacionado con una mejor capacidad de aprendizaje de palabras y mayor adquisición de vocabulario tiempo después (Gathercole, Service, Hitch, Adams, & Martin, 1999; Gathercole, Willis, Emslie, & Baddeley, 1992; Service, 1992).

Por otro lado, la repetición verbal es un recurso clave de las terapias de recuperación del habla en trastornos afásicos —caracterizados por la pérdida o dificultad para producir o comprender el lenguaje como consecuencia de un daño cerebral. De hecho, la capacidad de repetición verbal es uno de los dominios más utilizados para clasificar las afasias (Kertesz, 1979), lo cual permite agrupar a personas con un correlato comportamental y cerebral similar, y facilitar con ello la comunicación entre clínicos.

### **La repetición verbal como dominio para clasificar las afasias**

Una de las clasificaciones más usadas de los trastornos afásicos se basa en la capacidad de repetición verbal, distinguiendo las afasias con repetición alterada asociadas a lesiones perisilvianas de las afasias con repetición preservada asociadas a lesiones extra-

silvianas. Las afasias perisilvianas son más frecuentes e incluyen las afasias clásicas de Broca, Wernicke, conducción y global. Mientras que las afasias transcorticales, menos frecuentes, incluyen las afasias transcorticales motora, sensorial y mixta. Cada uno de estos subtipos se caracteriza por un perfil clínico y radiológico distinguible. Aunque una caracterización detallada excede los objetivos del presente resumen, se hará mención a la afasia de conducción y transcorticales (sensorial y motora) como representativas de afasias con repetición alterada y preservada, respectivamente.

La **afasia de conducción** se caracteriza especialmente por una notable dificultad en la repetición verbal, apareciendo más afectada la repetición de pseudopalabras que de palabras, y con relativa preservación de la capacidad de comprensión y producción verbal. Sin embargo, es frecuente que las afasias con repetición alterada cursen con dificultades más leves en la producción y en la comprensión del habla de forma asimétrica, por lo que algunos autores se refieren a estos tipos de afasia de conducción como afasia de conducción tipo Wernicke cuando aparece más afectada la comprensión, o afasia de conducción tipo Broca cuando aparece más afectada la producción. Otros síntomas característicos de la afasia de conducción son las parafasias fonémicas, así como la emisión de secuencias de aproximación a la palabra objetivo y autocorrección de errores (i.e., *conduite d'approche*). Este tipo de afasias se ha vinculado a un déficit en la programación del habla, una pobre codificación fonológica, así como a una alteración de la capacidad de integración audio-motora y de la memoria fonológica a corto plazo (Berthier, Lambon Ralph, Pujol, & Green, 2012). Desde el punto de vista neuroanatómico, la afasia de conducción se ha relacionado principalmente con lesiones del haz de sustancia blanca que une el área de Broca con el área de Wernicke, denominado fascículo arqueado (FA). Por otro lado, diversos estudios de neuroimagen también han señalado que una región de la corteza perisilviana conocida como área temporoparietal (Spt, por sus siglas en inglés) es clave para la integración audio-motora y su lesión resulta en un perfil de afasia de conducción (Buchsbaum et al., 2011).

Por otro lado, la **afasia transcortical sensorial** se caracteriza por déficits de comprensión verbal y denominación acompañados por repetición preservada y producción bien articulada, aunque el lenguaje suele ser ininteligible y lleno de parafasias neologistas. Por otro lado, la **afasia transcortical motora** es un tipo de afasia no fluente, que se presenta con dificultades en la producción y en la denominación, pero con repetición y comprensión preservadas. El habla suele estar acompañada de un marcado esfuerzo, agramatismos y dificultades articulatorias.

## Modelos neurocognitivos y bases cerebrales de la repetición verbal

Los modelos cognitivos, computacionales y neurocognitivos de repetición verbal convergen en postular que este proceso se sustenta en dos vías anatómica (vía dorsal y vía ventral) y funcionalmente (vía léxica y vía subléxica) segregadas (Dell, 1986; Hickok & Poeppel, 2004, 2007; McCarthy & Warrington, 1984; Patterson et al., 1987). Además, aunque no es fundamental para desempeñar la tarea, la repetición de un estímulo conlleva la imitación automática de algunos parámetros, como el ritmo o la melodía (Kappes et al., 2009) y de señales visuales (Iacoboni et al., 1999; Kohler et al., 2002). Por lo tanto, la repetición verbal se sustenta, por un lado, en una red cerebral especializada en el procesamiento lingüístico y por otro, en una red cerebral que, sin ser específica, tiene la capacidad de “activarse” cuando realizamos una acción (p. ej. hablar) y cuando la observamos. Este último sistema cerebral se conoce como sistema de *neuronas espejo* (Giacomo Rizzolatti & Craighero, 2004).

Más precisamente, uno de los modelos neurocognitivos más aceptados en neurociencia cognitiva —el modelo de la *doble ruta* de procesamiento— postula que la función de integración audio-motora, es decir, la capacidad para transformar un mensaje auditivo en un patrón motor, se sustenta principalmente en la vía de procesamiento *dorsal*. Por otro lado, los procesos de asociación léxico-semántico, es decir, los procesos que permiten acceder al significado de las palabras, están sustentados por un conjunto de estructuras que conforman la *vía ventral* (Hickok & Poeppel, 2004, 2007). De acuerdo con esta propuesta, la capacidad para repetir secuencias sin significado (pseudopalabras) recae principalmente sobre la vía dorsal (Dorothee Saur et al., 2008), mientras que ambas vías de procesamiento participarían en la repetición de palabras y frases con significado. A nivel anatómico, ambas vías de procesamiento nacen del giro temporal superior posterior (GTSp) donde tienen lugar los estadios tempranos del procesamiento acústico. La vía dorsal proyecta desde el GTSp a la corteza parietal inferior (CPI) y desde aquí a áreas frontales que participan en procesos articulatorios-motores, incluyendo el giro frontal inferior (GFI), la corteza premotora (CPM) y la corteza insular (CI). Por otro lado, la vía ventral proyecta desde el GTSp hacia el giro temporal posterior medio e inferior y desde aquí hacia el GFI (ver figura 6, Capítulo 1). Este modelo ha sido apoyado por cientos de estudios de resonancia magnética estructural y funcional en sujetos sanos (para una revisión ver Price, 2012), así como por estudios de lesión en personas con afasia (Fridriksson et al., 2016; Saur et al., 2008).

Por otro lado, el sistema de neuronas espejo se refiere a un conjunto de áreas cerebrales que responden tanto cuando se está escuchando o viendo a alguien hablar como cuando se ejecuta el habla, y abarca el GTSp bilateral, CPI, CPM and GFI izquierdo entre otros (Buchsbaum et al., 2001; Mashal et al., 2012). Por tanto, las áreas que comprenden la

vía dorsal postulada en el modelo de doble ruta se superponen con las áreas que conforman el sistema de neuronas espejo, lo que refleja la cercana interacción entre los procesos de repetición verbal y los de imitación; ambos fundamentales para el aprendizaje del lenguaje y para la recuperación de este en personas con afasia.

### *Evidencia de neuroimagen y estudios de lesión*

En línea con el modelo de la doble ruta de procesamiento, los hallazgos de estudios basados en sujetos sanos sugieren que la capacidad de repetición verbal se sustenta en una extensa red que involucra regiones corticales y diversas conexiones de sustancia blanca. De forma general, la repetición de palabras y pseudopalabras induce una fuerte activación bilateral del GTS, giro temporal medio (GTM) así como del GFI y giro frontal medio, en conjunto con áreas motoras primarias y CPM (Hartwigsen et al., 2013; Dorothee Saur et al., 2008; Yoo et al., 2012). Aunque en la repetición de ambos tipos de estímulos participan regiones similares, la repetición de pseudopalabras tiende a inducir mayor activación de la red fronto-temporal izquierda que la repetición de palabras, incluyendo el GTS, el GFI, la CI y la CPM (Hartwigsen et al., 2013; Palomar-García, Sanjuán, Bueichekú, Ventura-Campos, & Ávila, 2017; Saur et al., 2008). Algunos estudios también señalan que el patrón de activación inducido por palabras se extiende, en mayor medida que el de las pseudopalabras, hacia áreas posteriores del GTS (Yoo et al., 2012). De forma complementaria, los resultados de estudios de lesión en sujetos con afasia —a través de análisis de correlación entre la lesión en un área cerebral (p. ej. vóxel) y el rendimiento en una tarea (p. ej. repetición)— convergen con los resultados derivados de estudios con sujetos sanos (ver figura 10, capítulo1).

Las regiones corticales que forman parte de las redes que sustentan la capacidad de repetición están unidas por diferentes tractos de sustancia blanca que transcurren dorsal y ventralmente. Estudios basados en imagen por tensor de difusión han mostrado que la vía fronto-temporo-parietal, es decir la vía dorsal, comprende principalmente el fascículo arqueado (FA). Aunque inicialmente se describió como un haz de fibras que conecta la región de Broca con la región de Wernicke (Geschwind, 1970), estudios recientes ponen en evidencia que la estructura de este tracto es algo más compleja (Catani, Jones, & Ffytche, 2005). El FA está conformado principalmente por tres segmentos: (1) el segmento largo; (2) el segmento anterior; y (3) el segmento posterior. El segmento largo (vía directa) conecta directamente las áreas de Broca y Wernicke, mientras que los otros dos segmentos conforman una ruta indirecta entre estas dos regiones, donde el segmento anterior conecta el área de Broca con la CPI (territorio de Geschwind), y el segmento posterior vincula la CPI con el área de Wernicke. Por otro lado, la vía ventral abarca diferentes tractos de sustancia blanca

que conectan áreas frontales y temporales, incluyendo el fascículo fronto-occipital inferior (FFOI), el fascículo longitudinal inferior (FLI) y el fascículo uncinado (FU). El FFOI conecta la corteza orbitofrontal medial y lateral (AB47) con la parte posterior del GTS, GTM y GTI así como con la corteza occipital. El FLI conecta las mismas regiones posteriores temporales y occipitales que el FFOI con el lóbulo temporal anterior (Catani y Thiebaut de Schotten, 2008) y, por último, el FU conecta la corteza frontal dorsolateral y orbitofrontal con el lóbulo temporal anterior (Friederici y Gierhan, 2013). En general, las vías dorsales están lateralizadas a la izquierda y las ventrales muestran un volumen similar en el hemisferio derecho e izquierdo (Thiebaut de Schotten et al., 2011). Los tractos dorsal y ventral se muestran en la figura 9 (Capítulo 1).

Aunque las vías dorsal y ventral están segregadas anatómicamente y funcionalmente, algunos hallazgos sugieren que en ciertas circunstancias ambas vías cooperan sinérgicamente para ejecutar una tarea determinada (Makris y Pandya, 2009; Rauschecker y Scott, 2009; Rolheiser, Stamatakis y Tyler, 2011; Weiller, Bormann, Saur, Musso y Rijntjes, 2011). Por ejemplo, estudios previos de neuroimagen con población sana revelaron que, aunque en circunstancias normales la vía dorsal izquierda sustenta los procesos de repetición verbal (i.e., bucle fonológico) necesarios para aprender palabras nuevas presentadas de forma auditiva (López-Barroso, Catani, Ripollés, Dell'Acqua, Rodríguez-Fornells, y de Diego-Balaguer, 2013; López-Barroso, Ripollés, Marco-Pallarés, Mohammadi, Münte, Bachoud-Lévi, et al., 2015), la vía ventral izquierda puede hacerse cargo de esta función cuando la vía dorsal ipsilateral se bloquea artificialmente (p.ej. mediante la repetición de forma continuada de una sílaba irrelevante como “bla”) (López-Barroso, de Diego-Balaguer, Cunillera, Camara, Münte, Rodríguez-Fornells, 2011). Esto plantea varias preguntas importantes: (a) ¿las funciones de una vía pueden ser compensadas o respaldadas por la otra en determinadas circunstancias como las que se dan en el daño cerebral adquirido?; (b) ¿las posibles compensaciones son adaptativas, es decir, mejoran los déficits del lenguaje?; (c) ¿las capacidades lingüísticas extraordinarias en sujetos sanos expertos (p.ej. habladores inversos) son facilitadas por el reclutamiento de una vía alternativa no preferente para la función lingüística?; (d) ¿o por el contrario esta capacidad se sustenta en el remodelado de la vía preferente?. El potencial compensatorio de las vías relacionadas con el lenguaje es un tema de interés en el presente trabajo y se abordará en los estudios 1, 3, 4 y 5.

### **Dimorfismos sexuales en áreas homologas a las relacionadas con repetición verbal**

Un factor potencial de diferencias individuales en la estructura y función del cerebro es el sexo. Las diferencias asociadas al sexo en el cerebro humano han sido reconocidas desde hace más de un siglo (Woolley 1910). Se han publicado múltiples estudios de neuroimagen

sobre diferencias de sexo que examinan la estructura, los patrones de activación cerebral y la conectividad (ver Gong et al. 2011; Ruigrok et al. 2014; Sommer et al. 2002). Ruigrok y sus colaboradores realizaron un metaanálisis (Ruigrok et al. 2014) cuyos resultados sugieren que las mujeres tienen de promedio un mayor volumen en áreas del hemisferio derecho homólogas a las áreas del lenguaje relevantes para la repetición verbal (GFI derecho [pars triangularis y pars opercularis], planum temporale y circunvolución de Heschl). Además, los estudios de conectoma cerebral revelaron una conectividad intrahemisférica más fuerte en los hombres en comparación con las mujeres frente a una mayor conectividad interhemisférica en las mujeres en comparación con los hombres (Ingallhalikar et al. 2014; Sun et al. 2015).

En esta misma línea, evidencia previa sugiere que el volumen de los tractos de sustancia blanca relacionados con el lenguaje varía entre mujeres y hombres (Catani et al. 2007; Thiebaut de Schotten et al. 2011). Por ejemplo, la lateralización del FA puede estar sujeta a diferencias de sexo. Catani y colaboradores (2007) proporcionaron evidencia de que el segmento largo del FA está fuertemente lateralizado en términos de volumen hacia el hemisferio izquierdo en ~ 60% de la población estudiada, mientras que el ~ 40% restante tiene una representación bilateral. Además, los autores encontraron que el patrón bilateral era más frecuente en mujeres (~ 60%) que en hombres (~ 15%), mientras que la lateralización izquierda fuerte fue más frecuente en hombres (~ 85%) que en mujeres (~ 40%). En este sentido, dado que el FA aparece como una estructura importante para la repetición verbal, la lateralización de este tracto puede determinar la capacidad de repetición después de una lesión cerebral y la expresión clínica de los trastornos del lenguaje (Berthier et al. 2013; López-Barroso et al. 2015). De hecho, Forkel y colaboradores (2014) realizaron un estudio longitudinal prospectivo para evaluar cómo la lateralización del FA afecta la gravedad de la afasia post-ictus y su recuperación espontánea. Curiosamente, encontraron que el volumen del segmento largo de FA derecho era un factor predictivo de una mejor recuperación espontánea del lenguaje.

Por lo tanto, dado que las áreas corticales y los tractos de materia blanca del hemisferio derecho homólogos a las áreas críticas para la repetición verbal muestran mayor volumen en las mujeres que en los hombres, y dado que las diferencias anatómicas parecen desempeñar un papel importante en la expresión clínica y en la recuperación después del daño cerebral, será determinar si existen diferencias de sexo en la prevalencia de síndromes afásicos. Este tema se abordará en el Estudio 5 de la presente tesis doctoral, dónde la proporción de mujeres y hombres en dos tipos de afasia (una caracterizada por repetición reservada y otra por déficits de repetición) se estima en base a una revisión de la literatura de los casos publicados de afasia de conducción y afasias transcorticales.

## Objetivos

El objetivo transversal de la presente tesis doctoral ha sido explorar las características clínicas, cognitivas y neurales de la repetición verbal a partir de casos extremos en el continuo de su ejecución. Por tanto, se examinan las características asociadas a la repetición verbal tanto en sujetos con afasia como en sujetos con una habilidad fonológica extraordinaria denominada habla inversa. El presente trabajo comprende cinco estudios que de forma conjunta pretenden estudiar la flexibilidad de las vías del lenguaje y aportar evidencia que permita establecer en qué circunstancias las funciones de una vía pueden ser compensadas (en el caso de pacientes con afasia) o potenciadas (en el caso de personas con habilidades extraordinarias) por la otra vía para mejorar las funciones lingüísticas. De forma complementaria, esta tesis aborda problemáticas clínicas y pretende elucidar alternativas de evaluación y tratamiento para un síntoma afásico muy frecuente pero poco estudiado denominado ecolalia —caracterizado por la repetición excesiva de palabras y expresiones emitidas por otra persona. Finalmente, en este trabajo se han explorado fuentes de variabilidad en la capacidad de repetición verbal después de un daño cerebral, con especial interés en el sexo (hombres vs mujeres) como variable relevante. Los objetivos concretos de cada uno de los 5 estudios incluidos se exponen a continuación.

**Estudio 1** tiene como objetivo examinar si la ecolalia mitigada y la conducta de búsqueda (*conduite d'approche*) en tres casos de afasia post-ictus crónica surgen como compensación de una ruta (p. ej., dorsal) cuando la otra (p. ej., ventral) está afectada. Para este propósito, se utilizan evaluaciones multimodales que incluyen lenguaje y otras funciones cognitivas, así como neuroimagen multimodal (resonancia magnética y tomografía por emisión de positrones).

**El Estudio 2** tiene el objetivo de conocer el estado del arte del síntoma de ecolalia en el contexto de la afasia post-ictus, revisando las características de los diferentes tipos, sus posibles causas y correlatos cerebrales; y proporcionar aproximaciones para su evaluación clínica y tratamiento.

**El Estudio 3** tiene como objetivo estudiar más a fondo el subtipo más frecuente de ecolalia (i.e., ecolalia mitigada) en una persona con afasia fluida y comprensión auditiva alterada, para elucidar su funcionalidad, y explorar las características cerebrales que acompañan este síntoma. Dado que en este caso la ecolalia mitigada interfería con la comunicación funcional del paciente, un objetivo adicional fue estudiar la eficacia de un tratamiento (terapia intensiva del lenguaje y memantina) para reducir las instancias de ecolalia mitigada.



**El Estudio 4** tiene como objetivo identificar las características comunes y las diferencias individuales a nivel cognitivo y cerebral de dos sujetos sanos con la capacidad extraordinaria de invertir el habla, según lo evaluado mediante tareas de repetición hacia adelante y hacia atrás. De forma general y basado en un enfoque multidimensional, este estudio busca ofrecer información sobre las estrategias cognitivas y las características neuronales distintivas que caracteriza el desempeño sobresaliente en tareas lingüística basadas en funciones auditivo-motoras.

**El Estudio 5** tiene como objetivo analizar la distribución por sexo de dos tipos de afasias, una caracterizada por déficits de repetición verbal (i.e., afasia de conducción) y la otra caracterizada por repetición preservada (i.e., afasia transcortical), con el fin de proporcionar evidencia sobre si los problemas de repetición después del daño cerebral tienen diferente prevalencia en hombres y mujeres. La hipótesis de este estudio se basa en la evidencia de diferencias estructurales y funcionales entre hombres y mujeres en áreas cerebrales relacionadas con el lenguaje, especialmente del hemisferio derecho.

## **Resumen de los estudios, resultados y conclusiones**

Los comportamientos verbales repetitivos como la conducta de búsqueda (*conduite d'approche*) y la ecolalia mitigada son fenómenos bien conocidos desde las primeras descripciones de afasia. Sin embargo, no hay un conocimiento actualizado y sustancial sobre sus características clínicas, correlatos cerebrales y tratamiento. Por esto, centrándonos en diferentes aspectos de estos síntomas, los estudios 1, 2 y 3 han ido dirigidos a proporcionar datos que permitan profundizar en aspectos clínicos y en el conocimiento de los mecanismos neurales que dan lugar a estos comportamientos.

Específicamente, el **Estudio 1** aporta evidencia de que la conducta de búsqueda (o *conduite d'approche*) y la ecolalia mitigada no emergen como efecto directo de una lesión (tejido no funcional) en el hemisferio izquierdo, sino que representan procesos de plasticidad y compensación entre las vías dorsal y ventral de la repetición. Para explicar esta idea estudiamos tres casos de afasia fluida crónica que presentaban conducta de búsqueda, ecolalia mitigada y ambos síntomas, y exploráramos sus características clínicas y neurales. Usando neuroimagen multimodal, encontramos que la persona con conducta de búsqueda tenía lesiones que afectaban principalmente la vía dorsal izquierda, mientras que la persona con ecolalia mitigada presentaba principalmente afectación de la vía ventral izquierda. La coexistencia de conducta de búsqueda y ecolalia mitigada se asoció con afectación de áreas que se solapan con las descritas en los dos casos anteriores (figura 4, Estudio 1). Los resultados de este estudio sugieren que la conducta de búsqueda y la ecolalia mitigada reflejan

cambios dentro de la vía preservada del hemisferio izquierdo y vías alternativas del hemisferio derecho que surgen para compensar las funciones lingüísticas que anteriormente dependían de la actividad de la vía dañada. Así, la conducta de búsqueda emergería de la actividad de la vía ventral, tras daño de la vía dorsal, en un intento por compensar las funciones de la vía dorsal (p.ej., repetición verbal). De la misma forma la ecolalia mitigada reflejaría la actividad de la vía dorsal cuando existe daño en la vía ventral, en un intento por superar entre otros los déficits de comprensión verbal (frecuentes tras lesiones ventrales). Por lo tanto, la ecolalia parece emerger de la vía dorsal izquierda preservada (y componentes derechos) cuando la vía ventral está dañada. Probablemente, la conducta de búsqueda resulta de la actividad de la vía ventral cuando la vía dorsal izquierda está dañada. Aunque en la actualidad, estos comportamientos verbales repetitivos solo proporcionan un rendimiento subóptimo en personas con afasia, es decir, no contribuyen a una comunicación eficiente, la interpretación novedosa de estos comportamientos como intentos activos para superar un déficit de lenguaje, abre nuevas oportunidades para remodelar vías preservadas con intervenciones modernas (p. ej., estimulación cerebral no invasiva) que promuevan la recuperación.

El **Estudio 2** presenta el estado del arte del síntoma de ecolalia en la afasia post-ictus, revisando aspectos clínicos y cerebrales. El análisis de diferentes tipos de ecolalia nos lleva a concluir que la ecolalia constituye un síntoma heterogéneo y que los diferentes tipos pueden organizarse en un continuo de gravedad, en el cual las formas más leves presentan mayor capacidad comunicativa. Así también, este artículo proporciona recomendaciones para su evaluación y tratamiento, sugiriendo que se debe evaluar la capacidad comunicativa de la misma, e inhibir a través de estrategias de tratamiento en aquellos casos en los que la ecolalia interfiera con la calidad de la comunicación.

El **Estudio 3** se focalizó en estudiar un caso de afasia fluida caracterizado por múltiples instancias de ecolalia mitigada. La ecolalia mitigada representa uno de los subtipos más leves y frecuentes en afasia. Este síntoma ha sido visto históricamente (Pick, 1924) como una estrategia compensatoria dirigida a fortalecer la comprensión auditiva. Sin embargo, esta hipótesis y otros posibles déficits subyacentes a la ecolalia mitigada no se han evaluado en detalle hasta ahora. Por esto, en el presente trabajo hemos estudiado las características clínicas y neurales de un paciente con ecolalia mitigada. Puesto que en este caso las numerosas instancias de ecolalia interferían con la comunicación funcional, se evaluó la eficacia de la terapia intensiva del lenguaje y de un fármaco (memantina) para aminorar la ecolalia con la idea de mejorar la capacidad comunicativa del discurso. El paciente recibió 2 semanas de terapia intensiva del lenguaje seguida de administración de memantina. Se evaluó la ecolalia

en varios puntos antes y después del tratamiento. Se adquirieron imágenes de resonancia magnética estructurales y funcionales que permitieron hacer análisis de tractografía y de actividad cerebral mientras la persona repetía palabras y pseudopalabras. En el caso estudiado se muestra que la ecolalia surge principalmente como una estrategia para compensar los déficits de comprensión y las alteraciones de la memoria a corto plazo asociadas a una gran lesión temporal. El análisis de neuroimagen funcional y estructural sugirió que la ecolalia emerge de la actividad de los remanentes de la vía dorsal izquierda (figuras 3 y 5, Estudio 3) con compensación funcional en el hemisferio derecho. Además, los resultados de este estudio de caso único sugieren que la ecolalia que interfiere con la comunicación funcional puede ser modulada a través del tratamiento.

El **Estudio 4** investigó las características cognitivas y neurales de dos personas con una habilidad extraordinaria para invertir palabras y oraciones (¡de más de 10 palabras!) de forma rápida y precisa. Por ejemplo, dada la frase “sueña con ovejas eléctricas”, estos sujetos repetirían “añeus noc sajevo sacirtcéle” o “sacirtcéle sajevo noc añeus”. Este proceso implica la repetición de material auditivo, pero requiere de procesos intermedios de reordenamiento, lo que incrementa la demanda cognitiva. El estudio de esta peculiar habilidad nos permitió indagar en los mecanismos de procesamiento fonológico y más específicamente los mecanismos de secuenciación fonémica, es decir, los sistemas neurocognitivos que permiten organizar y mantener secuencias de fonemas específicas. Además, este modelo de pericia lingüística permitió explorar las peculiaridades cerebrales que sustentan este comportamiento extraordinario, y de forma más general informar sobre mecanismos de plasticidad. En este contexto, esperábamos que los habladores inversos presentaran diferencias estructurales y/o funciones en áreas y tractos de la vía dorsal —principal vía que sustenta los procesos de conversión audio-motora. No obstante, también consideramos que los habladores inversos requieran de recursos cognitivos/cerebrales adicionales, por lo que también se esperaba la contribución de las áreas y tractos de la vía ventral, o áreas implicadas en procesos de dominio general. Específicamente, este trabajo incluyó tareas conductuales (p.ej., memoria, repetición directa y repetición inversa, decisión léxica) junto con la caracterización cerebral a nivel estructural (morfometría basada en vóxeles y tractografía) y funcional (conectividad funcional en reposo), que fueron comparadas con un grupo control. Para el análisis de tractografía se consideraron tanto los tractos de la vía dorsal (FA) como ventral (FFOI, FLI y FU), mientras que para el análisis funcional se seleccionaron como regiones de interés áreas involucradas en procesamiento fonológico (GFI, CI, giro supramarginal, y GTSp). En comparación con los sujetos controles, ambos habladores inversos mostraron tener un rendimiento significativamente mejor en repetición inversa de palabras y frases. Además, esta

habilidad extraordinaria se acompañó de diferencias estructurales y funcionales a nivel cerebral. Aunque se observaron diferencias individuales entre los dos hablantes inversos, en general los resultados apuntan a adaptaciones estructurales y funcionales a lo largo de regiones y tractos de la vía dorsal, con soporte complementario de la vía ventral y áreas relacionadas con procesos de domino generales. Estas diferencias estuvieron caracterizadas por un mayor volumen de sustancia gris y una mayor integridad en regiones de la vía dorsal, y mayor conectividad funcional entre las áreas de interés y diferentes regiones cerebrales (Figuras 2 y 3, Estudio 4). Si bien a través de la evaluación cognitiva (memoria de trabajo, atención) realizada no se detectaron ventajas cognitivas asociadas a la pericia en tareas de repetición, especulamos que las diferencias cerebrales observadas están relacionadas con la estrategia utilizada durante los procesos de reordenamiento, probablemente basada en procesos de memoria fonológica en un caso y estrategias de visualización en el otro.

Finalmente, en el **Estudio 5** se realizó una revisión sistemática de la literatura para estudiar si la proporción de mujeres y hombres en la afasia de conducción difiere de la esperada por prevalencia de accidentes cerebrovasculares en cada uno de los sexos. Además, se revisaron los casos publicados de afasia transcorticales como grupo control. Los resultados de este estudio sugieren que la proporción de hombres en el grupo de afasias de conducción es mayor al esperado por prevalencia de accidentes cerebrovasculares, mientras que la proporción de mujeres es menor de la esperada. No se encontraron diferencias en el grupo de transcorticales (grupo control). Una posible interpretación de este hallazgo hace referencia a las diferencias cerebrales (anatómicas y funcionales) entre hombres y mujeres descritas anteriormente. Así pues, la existencia de un mayor volumen en áreas perisilvianas del hemisferio preservado y una mayor integridad del FA, conjuntamente con mayor conectividad interhemisférica que los hombres, podría favorecer la recuperación en mujeres mediante el reclutamiento de estructuras del hemisferio derecho.

De forma general, los resultados de los estudios que conforman esta tesis doctoral sugieren que las vías que sustentan la capacidad de repetición verbal, a pesar de tener especificidad funcional, trabajan sinérgicamente, de forma que si una de ellas no está disponible (p.ej., por daño cerebral) la otra vía ipsilateral y vías del hemisferio derecho intentan compensar las funciones dañadas, aunque quizás con menor eficacia. Concretamente, este trabajo sugiere que las estrategias cognitivas y los componentes cerebrales que sustentan algunas tareas cambian después del daño cerebral, y que los síntomas considerados previamente como "errores", pueden reflejar cambios plásticos en vías compensatorias. Así, proponemos que los síntomas de ecolalia y conducta de búsqueda representarían compensación de una vía (y vías alternativas del hemisferio derecho) cuando

la otra ha sido dañada. Es de destacar que el Estudio 3 sugiere que la ecolalia representa un intento por sobreponerse a otros déficits como dificultades de comprensión. No obstante, la eficacia de este mecanismo no está clara, y nuestros trabajos sugieren que en los casos en los que exista excesiva ecolalia y que, por tanto, esta interrumpa el flujo de la comunicación, debe ser tratada para disminuir las instancias. En el otro extremo, las habilidades lingüísticas extraordinarias (habladores inversos) parecen acompañarse de diferencias estructurales y funcionales que afectan principalmente a la vía optimizada para la tarea (p.ej. vía dorsal), con soporte adicional de otras vías (p.ej. ventral), y de áreas involucradas en procesos de dominio general. Pero es preciso destacar que existen importantes diferencias interindividuales en los mecanismos subyacentes, probablemente reflejo del uso de diferentes estrategias cognitivas. Así también, los resultados aquí expuestos sugieren que el sexo es una variable importante que influye en la capacidad de repetición después de un daño cerebral. Creo que los resultados y recomendaciones presentadas en esta tesis contribuyen a mejorar la comprensión de las redes cerebrales que sustentan la mejora de las habilidades lingüísticas, y el manejo clínico de algunos síntomas comunes de la afasia. Así también, los resultados de este trabajo pueden favorecer al desarrollo de modelo de plasticidad cerebral en modelos patológicos y en expertos.



# CHAPTER 6





## Chapter 6. References

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