

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



María José Torres-Prioris^{a,b,c,1,*}, Diana López-Barroso^{a,b,c,1,*}, Núria Roé-Vellvé^{d,e},
José Paredes-Pacheco^{d,f}, Guadalupe Dávila^{a,b,c}, Marcelo L. Berthier^{a,c}

^a Cognitive Neurology and Aphasia Unit, Centro de Investigaciones Médico-Sanitarias, Instituto de Investigación Biomédica de Málaga (IBIMA), University of Málaga, Málaga, Spain

^b Area of Psychobiology, Faculty of Psychology and Speech Therapy, University of Málaga, Málaga, Spain

^c Research Laboratory on the Neuroscience of Language, Faculty of Psychology and Speech Therapy, University of Málaga, Málaga, Spain

^d Molecular Imaging Unit, Centro de Investigaciones Médico-Sanitarias, General Foundation of the University of Málaga, Málaga, Spain

^e Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain

^f Molecular Imaging and Medical Physics Group, Department of Psychiatry, Radiology and Public Health, University of Compostela, Galicia, Spain

ABSTRACT

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, &

* Corresponding authors at: Unidad de Neurología Cognitiva y Afasia, Centro de Investigaciones Médico-Sanitarias (CIMES), Universidad de Málaga, C/Marqués de Beccaria 3, 29010 Málaga, Spain.

E-mail addresses: mjprioris@uma.es (M.J. Torres-Prioris), dlopbarroso@uma.es (D. López-Barroso).

¹ These authors have contributed equally to this work.

Lambon Ralph, 2018; Tyler, Marslen-Wilson, & Stamatakis, 2005), tractography-based analysis (Basilakos et al., 2014; Geva, Correia, & Warburton, 2015) and connectome-based lesion-symptom mapping (Gleichgerrcht, Fridriksson, Rorden, & Bonilha, 2017). However, to date few studies have focused on the neural mechanisms underpinning different types of speech errors including RVBs (Fridriksson et al., 2009; Lee, Zreik, & Hamilton, 2017; Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018; Ueno & Lambon Ralph, 2013; Berthier, Torres-Prioris et al., 2018). According to these studies, residual language deficits usually emerge from lesions affecting cortical and subcortical areas and from the breakdown of different white matter tracts that support language functions. In this line, lesions to the main dorsal pathway, the arcuate fasciculus (AF), are mostly related to deficits in repetition, phonological processing, object naming, and speech fluency (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013; Geva et al., 2015). On the other hand, lesions affecting the ventral pathway (inferior fronto-occipital fasciculus [IFOF], inferior longitudinal fasciculus [ILF], uncinate fasciculus [UF]) are mostly related to comprehension and naming deficits as well as reduced fluency (Basilakos et al., 2014; Fridriksson et al., 2013; Kümmeler et al., 2013).

Although language function relies on the activity of a widely distributed and redundantly connected neural systems (López-Barroso & de Diego-Balaguer, 2017; Mesulam, 1990), in the healthy brain some of these systems may be more efficient than others due, in part, to their repetitive use. This means that the existence of distributed anatomical systems for a given function provides the brain with a powerful capacity of resilience and recovery after focal brain damage (Friston & Price, 2003). In this context, when all sets of neural systems underlying a specific verbal function are damaged, this behavior would be lost or severely disturbed, as evidenced by the presence of residual language deficits. However, when only the preferred/more efficient system is damaged, there are still other routes that may subserve that specific behavior (Noppeney, Friston, & Price, 2004). This implies that this behavior may still occur although hindered by reduced accuracy, delayed response times, or both. We propose that in PWA, RVBs are compensatory behaviors that emerge from dynamic plastic changes undergoing after brain damage and these might be interpreted as adaptive neuroplastic changes, rather than considering them an example of maladaptive plasticity (Spielmann, Durand, Marcotte, & Ansaldi, 2016). Nevertheless, the emergence of speech errors in structured contexts (i.e., intervention) may be beneficial (Ownsworth et al., 2017) and necessary to guide these neural changes and promote a more optimal outcome.

Conduite d'approche (CdA) and mitigated echolalia (ME) are two understudied RVBs frequently present in PWA. Thus, we will take them as examples of the proposed idea of compensatory behaviors and, based on three clinical cases, we will analyze the putative neural underlying mechanisms. For this, in the next section we first outline the clinical characteristics of CdA and ME and refer to the available literature on the neural networks mediating these RVBs. Second, we analyze the extant evidence coming from subjects with brain lesions and healthy subjects that support the hypothesis of RVBs as compensatory behaviors that rely on the activity of alternative undamaged neural networks. Third, we present behavioral and neuroimaging data from 3 PWA showing CdA, ME and both symptoms.

1.1. Conduite d'approche and mitigated echolalia

The French term CdA refers to successive and self-initiated approximations to a target word in an attempt to correct phonemic errors in different contexts (spontaneous speech, repetition or naming). Therefore, a highly variable sequence of phonemic approximations may be emitted, leading in some occasions to the target word (Christman, Boutsen, & Buckingham, 2004; Joanette, Keller, & Lecours, 1980;

Sollereder, Stark, & Pons, 2013). Not rarely, attempts at phonemic approximations are unsuccessful to reach the desired word (Ueno & Lambon Ralph, 2013) to the extent that the resulting fragmentary emissions may move farther away from the target word. This behavior, known as *conduite d'ecart* or iteration, mainly occurs in cases of recovered Wernicke's aphasia with reduced monitoring of speech production (Christman et al., 2004; Kleist, 1931). Although the mechanisms underpinning self-awareness and self-repair of errors in CdA and *conduite d'ecart* are still unknown, the former behavior can be interpreted in the domain of the state feedback control model (Hickok, Houde, & Rong, 2011). This model, which comprises auditory-motor processes reliant on the activity of the left posterior Sylvian fissure at the parietal-temporal area and dorsal language stream, proposes that the motor command required to articulate a given word triggers an internal model of the sensory-acoustic consequences of this command (forward prediction). This cognitive operation supports not only an online monitoring function required to pronounce correctly the target word, but it also provides feedback to update this command and, therefore, self-correct errors online (Hickok et al., 2011; Hickok & Poeppel, 2015). When a focal lesion affects the regions in charge of the internal monitoring of the motor commands, the external sensory feedback is required for self-detection and, hence, error correction. In this context, CdA may emerge after the disruption of the internal monitoring mechanism, thus implying that only the external feedback, once the word has been actually produced, may be used to correct the motor command when necessary (Hickok et al., 2011). It seems that error detection and the subsequent "clean up" of noisy phonemic approximations are possible via activation of auditory targets in the lexical-semantic system (ventral language stream) (Hickok & Poeppel, 2016; Nadeau, 2001; Ueno & Lambon Ralph, 2013).

The other frequent RVB, echolalia, refers to the repetition of words, non-words and/or utterances spoken by another person (Wallesch, 1990). Various types of echolalia can be identified moving in a continuum of severity from impulsive and non-communicative verbal echoing (e.g., ambient and automatic echolalia) to a more voluntary and indolent repetition (e.g., ME) (for review, see Berthier, Dávila, & Torres-Prioris, 2018; Berthier, Torres-Prioris, & López-Barroso, 2017). Subjects with ambient echolalia automatically repeat words and sentences not directed to them, but coming from unrelated conversations around them or from other sources (e.g., TV, radio) thus possibly implying a breakdown of self-other distinction and higher order social-cognition skills (mentalizing) (Berthier et al., 2017; Fisher, Burd, & Kerbeshian, 2008; Frith & Frith, 2012; Suzuki, Itoh, Hayashi, Kouno, & Takeda, 2009). The other subtype of severe echoing is termed automatic echolalia and it occurs when subjects are directly addressed by interlocutors, and not when questions and comments are directed to other people. Both subtypes usually result from extensive damage to the left medial prefrontal cortex which, besides reducing voluntary speech production, can increase cortical excitability of the left inferior frontal gyrus automatically heightening sensory-motor translation of speech repetition (Restle, Murakami, & Ziemann, 2012), thus favoring verbal echoing (Berthier et al., 2017). A less severe subtype, ME, refers to the echoing of a just heard word or sentence introducing some change, for instance in person, time or verb conjugation (Pick, 1924). Although ME usually entails a communicative intention, it may not always be purposeful (Berthier, Torres-Prioris et al., 2018). Traditional descriptions of ME considered that words or phrase fragments that sound ambiguous, equivocal, or are poorly understood are repeated to improve meaning access (Pick, 1924; Stengel, 1947). In addition, ME might also be produced for related reasons associated with fragile comprehension such as recapitulate meaning, regain attention, or take time to plan a response which may variously result from impaired short-term memory or inefficient inhibitory mechanisms (Berthier et al., 2017). It is noteworthy that in contrast with more severe subtypes of echolalia, ME can

also be present in fluent aphasias with impaired repetition (Wernicke's, conduction and word-meaning deafness)² resulting from damage to the perisylvian language region (see Berthier, Dávila, et al., 2018 for review).

The expression of CdA and ME undoubtedly requires verbal production or repetition of phonemic sequences and words-short phrases, respectively. The ideal candidates for mediating these RVBs are two functionally segregated language streams supporting language processing: *dorsal* and *ventral*. The *dorsal* stream, connected through the AF (Catani, Jones, & Ffytche, 2005; Catani & Mesulam, 2008; Turken & Dronkers, 2011), is responsible for the translation of the sensory/acoustic speech signals into motor-articulatory representations (i.e., auditory-motor integration) (Hickok & Poeppel, 2007). Thus, the AF represent the main pathway for verbal repetition, especially for non-words (Saur et al., 2008; Sierpowska et al., 2017), and therefore for the learning of new phonological word forms (López-Barroso et al., 2013). The *ventral* stream comprises regions in the ventrolateral prefrontal cortex and the middle and superior temporal cortices and is connected through different ventral pathways such as the IFOF, the ILF and probably the UF. The ventral stream is preferentially involved in the mapping between sensory/acoustic speech signals onto conceptual and semantic representations, subserving verbal repetition of known words (Nozari & Dell, 2013). Despite the preferred labor of each stream (Makris & Pandya, 2009; Rauschecker & Scott, 2009; Rijntjes, Weiller, Bormann, & Musso, 2012; Rolheiser, Stamatakis, & Tyler, 2011; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011), both dorsal and ventral streams operate in concert to successfully accomplish a given task (Hope et al., 2014; López-Barroso et al., 2015; López-Barroso & de Diego-Balaguer, 2017; Mesulam, 1990). Therefore, it is crucial to explore whether under irreversible damage, the preferred function of one stream can be compensated by the other, and whether this compensation is either sufficient to improve language deficits, intermittently successful to access to target verbal material, or if it negatively affects language performance. We hypothesize that CdA and ME are active compensatory efforts for overcoming residual language deficits that may rely on adaptive neural changes within undamaged or compromised but viable neural networks. In the next section we analyze the available evidence that supports our hypothesis.

1.2. Conduite d'approche and mitigated echolalia as compensatory behaviors

Recently, it has been suggested that CdA and ME are supported by the activity of the remnants of the damaged white matter tracts in the left hemisphere together with variable compensatory activity of other tracts in both cerebral hemispheres (Berthier, Torres-Prioris et al., 2018; Forkel et al., 2014; Ueno & Lambon Ralph, 2013). Using a neuroanatomically constrained dual dorsal-ventral streams computational model of CdA, Ueno and Lambon Ralph (2013) provided preliminary evidence that successful CdA after experimental damage to the dorsal stream was supported partly by the intact ventral lexical-semantic stream. In the same line, functional changes in left temporal perilesional areas were found to be related to speech errors reduction after anomia treatment in PWA (Fridriksson, Richardson, Fillmore, & Cai, 2012).

Further evidence supporting compensation of one stream when the other one is not fully available comes from previous studies of subjects with brain lesions (Berthier, Torres-Prioris et al., 2018; Rauschecker et al., 2009; Yeatman & Feldman, 2013), healthy children (Brauer,

Anwander, & Friederici, 2011), and healthy adults (López-Barroso, de Diego-Balaguer, Cunillera, Camara, Münte, & Rodriguez-Fornells, 2011). For instance, some examples of these mechanisms are found in the aphasic literature. Thus, in a reported case of a person with trans-cortical motor aphasia and partial damage to the left AF, multimodal neuroimaging suggested that successful repetition of words, three-word lists, and sentences was achieved through redirection of verbal information via the spared temporo-parietal segment of the AF to the ventral stream (Berthier et al., 2013). In addition, a multimodal imaging study of a subject with a residual Wernicke's aphasia showed that ME was supported by the activity of remnants of the left dorsal stream and the intact right dorsal stream that aimed to compensate the severe damage to the left ventral stream (Berthier, Torres-Prioris et al., 2018).

Further convergent evidence comes from other cases of subjects with brain lesions. A study reported the case of an adolescent girl with absence of the fronto-temporal and the fronto-parietal segments of the AF due to a perinatal bilateral periventricular leukomalacia who had average scores in expressive language and repetition abilities as a consequence of increased ventral pathway connectivity (Yeatman & Feldman, 2013). In another study, Rauschecker and collaborators (Rauschecker et al., 2009) reported the case of a teenager with radiation-induced necrosis affecting mainly the white matter (brain radiation therapy was given at age of 5). At age of 15 years, she had profound dyslexia but her language and repetition skills were preserved. Neuroimaging disclosed a normal left-lateralized activation pattern during language processing despite having absence of AF and superior longitudinal fasciculus in both hemispheres. Interestingly, the ventral pathways were intact, suggesting that the connectivity between frontal and posterior temporal cortices were carried out ventrally.

Additional evidence of compensation of the ventral pathway over the dorsal one comes from healthy subjects. A longitudinal developmental neuroimaging study (Brauer et al., 2011) demonstrated that 7-year-old children rely more on the ventral pathway during an auditory language processing task than adults, implying that in children the dorsal pathway, which is still immature, is not sufficient to perform the task and require the additional support of the ventral pathway. Moreover, in a diffusion tensor imaging study, López-Barroso and colleagues (López-Barroso et al., 2011) requested healthy participants to learn new auditory-presented words while they were required to continuously utter the syllable "bla" (articulatory suppression condition). The study reported that better word learning performance, which in normal circumstances relies over the dorsal pathway (López-Barroso et al., 2013; López-Barroso et al., 2015), was associated with greater white matter integrity of the ventral pathway. Noteworthy, performance was reduced compared to a condition without articulatory suppression, suggesting that although ventral compensation allowed participants to achieve a modest performance, results were suboptimal (López-Barroso et al. 2011).

Taken together, all this evidence supports the idea that a specific white matter pathway may represent the automatically eligible route in charge of successful behavior. However, in adverse conditions (i.e., brain damage, interference, immaturity) other latent systems might attempt to compensate for the unavailability of the preferred pathway. Following this line of reasoning, CdA may reflect the activity of the ventral pathway when the dorsal one is damaged (Ueno & Lambon Ralph, 2013), while ME may represent an overreliance on the dorsal route when the ventral is impaired (Berthier, Torres-Prioris et al., 2018). However, compensation by the contralateral undamaged right hemisphere has also been found (Berthier, Torres-Prioris et al., 2018). The recruitment of the contralateral hemisphere may depend on different individual factors including, for example, whether the right hemisphere was part of the language network underlying repetition before brain damage. Accordingly, the study of RVBs like CdA and ME can inform how perilesional and remote parts of a damaged brain are reorganized in order to readjust the activity and to compensate the deleterious effect of brain damage. It is also evident that lesions do not respect anatomical boundaries and frequently brain damage partially or

² Word-meaning deafness is a rare aphasic symptom in which the ability to repeat words is relatively preserved without understanding their meaning (Kohn & Friedman, 1986). Auditory comprehension is abnormal, but comprehension of written language is normal (Bormann & Weiller, 2012). The deficit in auditory comprehension is secondary to a dissociation between accurate phonological and semantic information.

fully involves both transmission routes. Thus, in order to get further knowledge on the behavioral complexity and brain correlates of CdA and ME, it is also important to explore if both RVBs can coexist in the same aphasic subject (cf. Brown, 1975).

In the present study, we aimed to explore the language characteristics and structural and metabolic signatures of RVBs in three PWA showing either CdA (Subject 1), ME (Subject 2), or both CdA and ME (Subject 3). We sought to further investigate whether RBVs result from the compensatory interplay between preserved perilesional and bilateral remote cortical areas through the recruitment of alternative white matter tracts. This being the case, such RVBs most likely represent an attempt to overcome the residual language deficits induced by a lesion in the preferred/more efficient language route. Specifically, given the leading role of the dorsal stream in verbal repetition, we hypothesize that ME reflects an overreliance on this language pathway to compensate for a damage on the ventral stream and the resulting language deficits (e.g., impaired semantic access). Complementary, CdA results from the activity of the ventral pathway to overcome the linguistic impairment caused by a lesion on the dorsal one. Additionally, we examined for the first time the neural basis of concomitant ME and CdA.

To evaluate these compensatory behaviors, we used two different neuroimaging techniques: structural magnetic resonance imaging (MRI) and [18]-fluorodeoxyglucose positron emission tomography (18FDG-PET). MRI was used to delineate the structural lesion (at grey and at white matter levels), and 18FDG-PET was performed to study resting metabolic activity in the language brain system as a surrogate marker of the potential recruitment of these areas during any language task.

2. Methods

2.1. Index cases

Three Spanish monolingual subjects with chronic fluent aphasia were selected from the database of the Unit of Cognitive Neurology and Aphasia based on their differing patterns of RVBs and availability of multimodal neuroimaging data. Speech production in Subject 1 was characterized by numerous instances of CdA, Subject 2 presented predominantly ME's instances, and Subject 3 had both CdA and ME. All subjects were evaluated with the Western Aphasia Battery (WAB; Kertesz, 1982; Kertesz, Pascual-Leone, & Pascual-Leone García, 1990). In addition, subjects were assessed with different production tasks that elicited CdA and ME (see Table 1). Subject 1 was tested with selected subtests of the EPLA (Evaluación Psicolingüística en la Afasia) (Valle & Cuetos, 1995) (repetition [7 and 8] and naming [52]), which is the Spanish version of the Psycholinguistic Assessments of Language Processing in Aphasia; PALPA (Kay, Lesser, & Coltheart, 1992), picture naming of the Birmingham Object Recognition Battery (BORB) (Riddoch & Humphreys, 1993) and selected action verbs of the Object and Action Naming Battery (Druks & Masterson, 2000). In addition to the WAB, Subject 2 completed definition of selected words from the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1988). Finally, Subject 3 also performed repetition subtests (7, 8, 9, and 11) and Naming by Frequency subtest (52) from the EPLA. The subtest of Sentence Repetition (EPLA 12) could not be fully applied to Subject 3 because he could only repeat the subject of the sentence. Definition of selected words from the Vocabulary subtest of the WAIS (Wechsler, 1988) was also administered to this subject. A detailed description of the index cases and their linguistic profile is presented in the results section.

2.2. Neuroimaging method

2.2.1. Structural magnetic resonance imaging acquisition

MRI studies were performed on a 3-T MRI scanner (Philips Intera, Best, The Netherlands) equipped with an eight-channel Philips SENSE head coil. Head movements were minimized using head pads and a forehead strap. High-resolution T₁ structural images of the whole brain

were acquired with three-dimensional (3D) magnetization prepared rapid acquisition gradient echo (3D MPRAGE) sequence (echo time (TE): 4.6 ms; repetition time (TR): 9.9 ms; acquisition matrix: 240/200; field of view: 240; turbo field echo (TFE) factor: 200; flip angle: 8°; reconstruction voxel size: 1 mm × 0.94 mm × 0.94 mm). One hundred ninety contiguous slices, 0 mm slice gap, were acquired. The total acquisition time of the sequence was about 170 s. Structural brain scans were acquired for all three subjects and for 24 healthy controls (mean age: 55,75 ± 5,32 years; range: 48–67 years).

2.2.2. Lesion-based approach to mapping disconnection

In order to measure the direct and remote effect of the brain lesions in the different white matter tracts, we used two different tools part of the BCBtoolkit (<http://toolkit.bcblab.com>) (Foulon et al., 2018): Tractotron and Disconnectome map, respectively. First, lesion masks depicting the precise boundaries of the damaged areas were manually drawn for each subject on high-resolution T₁-weighted images in native space using MRICron software (Rorden & Brett, 2000). Binarized lesion masks and T₁-weighted images were normalized to the MNI152 standard space using Statistical Parametric Mapping (SPM12) software (Wellcome Department of Imaging Neuroscience, University College, London, UK, www.fil.ion.ucl.ac.uk/spm/). Cost function masking was used to improve non-linear normalization of damaged brains (Brett, Leff, Rorden, & Ashburner, 2001). T₁-weighted images were segmented into different tissues, and the normalization parameters derived from the segmentation were used for the normalization of the T₁-weighted images and the lesion masks.

After these procedures, Tractotron was used to automatically compute the percentage of overlap between the normalized brain lesion of each subject and each tract of interest (direct effect of the lesion). Tractotron uses tractographic reconstructions of targeted white matter pathways obtained from a group of healthy controls (Rojkova et al., 2016). Then, it quantifies the severity of the tract disconnection by measuring the probability of a given tract to be directly intersected by the lesion and the proportion of the given tract that is compromised (Thiebaut de Schotten et al., 2014). As a surrogate measure of tract damage, an index of lesion load (the proportion of the tract affected by the focal lesion) was used. However, whereas this measure is useful to explore the clinical implications of tract damage, it does not indicate indeed if the lesion is affecting a critical part of the tract, which could result in a complete disconnection (Hope, Seghier, Prejawa, Leff, & Price, 2016). Thus, in addition to the proportion of damage - or lesion load - (Hope et al., 2014; Marchina et al., 2011), the specific part of the tract that is affected by the lesion was also taken into account. Tractotron analyses were performed over an a priori selected set of language-related tracts, specifically the AF including its three segments (fronto-parietal or anterior, the temporo-parietal or posterior and the fronto-temporal or long segments) was analyzed as dorsal pathway, whereas the ILF, the UF and the IFOF were selected as ventral pathways.

In addition, to evaluate the remote effects caused by the focal brain lesion, the Disconnectome map tool was used. The Disconnectome map uses the normalized brain lesions as a seed to track streamlines in a normative diffusion weighted imaging tractography dataset, resulting in a probabilistic map of disconnection for each subject (Foulon et al., 2018). Hence, the resulting map indicates a probability of disconnection from 0 to 100% for a given lesion (Thiebaut de Schotten et al., 2015). Results are shown using a probability of disconnection equal or major than 0.90.

2.2.3. PET image acquisition

PET data acquisitions were performed on a Discovery ST PET/CT camera (General Electric, Milwaukee, WI) after an intravenous injection of about 3.3 MBq/Kg in 24 healthy controls and 2.4 MBq/Kg in index aphasic subjects. Transaxial and axial scanner resolution at the center of field of view were 6.1 and 5.6 mm full width at half maximum (FWHM),

Table 1
Cognitive and language testing for the 3 index cases.

	Digit span (forward)	Cognitive Testing	Subject 1: AFR			Subject 2: ASL			Subject 3: MFM		
			3	6	5	6	Instances of CdA [proportion]*	Scores [proportion]*	Instances of echoing [proportion]*	Scores [proportion]*	Instances of CdA and echoing [proportion]
Western Aphasia Battery (WAB)											
Aphasia Quotient (AQ)			71.1 [71]				55.6 [56]			61.9 [62]	
Spontaneous Speech (total score) (max: 20)			14 [70]				9 [45]	1 [17] ^b		15 [75]	
Information Content (max: 10)			8 [80]				4 [40]	-		7 [70]	
Fluency (max: 10)			6 [60]				5 [50]	-		8 [80]	
Auditory Verbal Comprehension (total score)			8.65 [8.86]				6.1 [61]	-		6.35 [63]	
Yes/No Questions (max: 60)			57 [95]				45 [75]	-		4 [20] ^b	
Auditory Word Recognition (max: 60)			53 [88]				39 [65]	10 [16] ^b		53 [88]	
Sequential Commands (max: 80)			63 [79]				38 [47]	4 [36] ^b		29 [36]	
Repetition (max: 10)			6 [60]				9.8 [98]	-		7 [70]	
Naming and Word finding (total score) (max: 10)			6.9 [69]				2.9 [29]	-		2.6 [26]	
Object Naming (max: 60)			47 [78]				16 [27]	-		12 [20]	
Word Fluency (max: 20)			4 [20]				1 [05]	-		4 [20]	
Sentence Completion (max: 10)			10 [11]				6 [60]	-		6 [60]	
Responsive Speech (max: 10)			8 [80]				6 [60]	-		4 [40]	
Psycholinguistic Assessments of Language Processing in Aphasia¹											
Repetition: Syllable length (EPLA 7)			22 [92]				4 [17] (2)	-		<u>24 [10]</u>	2 [08] (2) ^c
Non-Word Repetition (EPLA 8)			5 [20]				1 [04] (0) ^a	-		21 [87]	-
Repetition: Imageability × Frequency (EPLA 9)			-				-	-		73 [91]	11 [14] (6) ^c
Repetition: Morphology (EPLA 11)			-				-	-		55 [91]	2 [03] (1) ^d
Picture Naming × Frequency (EPLA 52)			46 [77]				18 [30] (8)	-		14 [23]	15 [25] (7) ^c
Auditory Lexical Decision: Imageability × Frequency (EPLA 5)			-				-	-		135 [84]	51 [31] ^b
Picture Naming, Birmingham Object Recognition Battery (BORB)			48 [63]				13 [17] (8)	-		-	-
Object and Action Naming Battery²			18 [90]				6 [30] (5)	-		-	-
Word definition task (max = 50) ³			-				30 [60]	23 [92] ^e		25 [50]	11 [44] ^b
											1 [04] (0) ^c

*Proportion of the maximum possible score. CdA indicates *conduite d'approche*. Numbers in brackets represent proportions. Numbers in parentheses indicate instances of successful CdA even in Subject 3. ^a CdA of a lexicalization (for the target non-word “rafé” the patient said “ca-ca-cafe” (coffee in Spanish). ^b Indicates Mitigated Echolalia. ^c Indicates Automatic Echolalia. ^d The Spanish version (EPLA) was used. ^e 20 selected items were administered. ³Definition of 25 selected words of the Vocabulary subtest of the WABs. Note that possible score in each item of the word definition task was from 0-2 definitions; the task was corrected by two independent evaluators and final scores reached by consensus. Scores obtained by each subject in the three linguistic domains used to classify aphasia subtype are highlighted. Note that almost all scores shown are below-average for a healthy subject, except for the ones underlined. Scores reflecting more severely affected domains (performance < 50%) are indicated in bold.

respectively. PET images were reconstructed using a 3D FORE-IR algorithm with CT attenuation correction (Matrix size, $128 \times 128 \times 47$; voxel size, $2.34 \times 2.34 \times 3.27$ mm).

2.2.4. PET analysis

Spatial preprocessing and statistical analysis of the PET images were performed with Statistical Parametric Mapping (SPM12), running on MATLAB R2016b (Mathworks Inc., Natick, MA, United States). All T_1 -weighted structural images and [^{18}F]-FDG PET images were manually aligned to anterior-posterior commissure (ACPC space). The reoriented PET images were co-registered with the T_1 -weighted scans. A lesion mask was drawn and applied over the T_1 -weighted images of each subject before normalization onto the MNI template (McGill University, Montreal, Canada). The obtained deformation fields were then applied to the coregistered PET volumes, with a final voxel size of $2 \times 2 \times 2$ mm. The normalized PET studies were smoothed with a FWHM 8-mm Gaussian kernel. Histogram-based intensity normalization was performed using an in-house software. In this procedure, the smoothed images of each subject were divided by the mean of the smoothed images of the healthy controls. Histograms of these masked ratio images were generated, excluding damaged areas and ventricles. Each smoothed PET study was then divided by the most prevalent value in the ratio image.

SPM analysis was carried out with the resulting PET studies. Areas of hypometabolism and hypermetabolism were estimated for each subject with the contrasts aphasic subject < healthy controls and aphasic subject > healthy controls, using a 2-sample *t*-test model. A statistic threshold of $p < 0.05$ (FWE corrected) was applied. The resulting SPM (*t*) images were masked to include only white matter and grey matter areas in the analysis.

3. Results

3.1. Index cases: clinical information and language profile

Subject 1: *Conduite d'Approche*

Subject 1, AFR, was a 43-year-old right-handed male who suffered a large left temporo-parietal and posterior insular infarction. Before the stroke, he worked as a technical architect. In the acute post-stroke period, he had a right hemiparesis and a fluent aphasia with comprehension deficits (Wernicke's aphasia). During the subacute and early chronic periods, he received conventional speech-language therapy and physiotherapy. At the time he was referred to our unit (29 months after onset), he had an Aphasia Quotient in the WAB of 71.1 (see Table 1). His pattern of aphasia was consistent with a *reproduction CA*³ (Gvion & Friedmann, 2012; Nadeau, 2001; Shallice & Warrington, 1977). The spontaneous speech of AFR was moderately fluent, but frequently interrupted by word retrieval problems and punctuated by phonemic paraphasias and overt attempts of errors self-correction (CdA), reflecting conscious awareness and monitoring of speech output. Auditory comprehension was mildly impaired for auditory word recognition (body parts) and understanding of sequential commands only for long sentences. Importantly, repetition was preserved for words (EPLA 7), but markedly impaired for nonwords (EPLA 8). Sentence repetition was mildly impaired for short phrases and severely impaired for long sentences, failing to repeat the last items; the latter finding reflect deficits in syntactic comprehension and, mostly, in auditory-verbal short-term memory, functions mostly supported by the dorsal stream (i.e. AF)

³ Reproduction conduction aphasia, also known as output conduction aphasia, is characterized by the generation of phonemic errors in all production tasks (naming, repetition, oral reading), caused by a post-lexical deficit. All production tasks results in phonologically-related non-words, often adopting the characteristic of CdA. Auditory comprehension is preserved except for syntactically complex sentences.

(Friederici, 2012). Occasionally, his poor performance in sentence repetition reflected an inability to retain phonological information and reliance on lexical-semantic processes (Baldo, Klostermann, & Dronkers, 2008). For example, when hearing a sentence of the WAB (sentence 11: "The telephone is ringing") he repeated: "The telephone is call.... calling". His memory span for digits was 3 items. Picture naming was moderately impaired (Table 1).

During language testing it was noted that AFR had multiple instances of CdA in naming pictures depicting nouns and verbs and, to a lesser degree, in single word and sentence repetition (see Table 1). Phonemic approximations to the target word sometimes led to the correct response (see Table 1) (i.e., target noun: "elephant"; AFR response: "eli... elipa... eliphan... iliphan... ephe... a... eli... aliphant... ile... elephant!"), whereas other attempts were unsuccessful, and the repetitive productions moved farther away from the target (i.e., target noun: "gorilla (or orangutan)"; AFR response: "monkey... but is not... is orin... oro... oringoran.").

Subject 2: *Mitigated Echolalia*

The subject, ASL, was a 53-year old right-handed male, previously working as a risk prevention engineer, who suffered a severe traumatic brain injury after falling off a bike. An emergency brain computerized tomography scan revealed a left temporo-parietal epidural hematoma. He underwent an emergency craniotomy for evacuation of the hematoma and during surgery, several small contusion foci were identified in the temporal lobe. In the post-operative period, he had a right hemiparesis with dystonic right hand posturing as well as language, attention, memory and executive deficits. ASL received speech-language therapy and physiotherapy. Although he showed some improvement, multi-domain cognitive deficits were still present at the time of referral to our unit. The evaluation presented here was performed 4 months after onset. By that time, his Aphasia Quotient of the WAB was 55.6 and the language profile was compatible with a transcortical sensory aphasia (Table 1). His spontaneous speech was fluent and very perseverative, but slow and scarce giving a halting impression, which was conditioned by the frequent occurrence of word finding difficulties and filler exclamations ("I've not hit a single one!"). Auditory comprehension abilities were moderately impaired. ASL had problems to both answer questions and comprehend sequential commands due to inability to grasp the meaning of long sentences. Semantic comprehension for single words was also moderately impaired showing more difficulties with the recognition of body parts and right-left discrimination on his own body. These findings suggest impairments in auditory-to-meaning mapping, function mainly relying on the ventral language pathway (Friederici, 2012). This contrasted with his repetition ability, which was almost flawless. His memory span for digits was fully preserved (6 items). Picture naming was severely affected since he was unable to name most stimuli.

During testing, ASL presented automatic echolalia for single words; for example, in the Auditory Word Recognition subtest of the WAB when asked to point to a target, he provided a verbatim repetition of the stimulus just said by the examiner. However, it is worth noting that he mainly produced ME in other contexts. Instances of ME were mainly heard in demanding comprehension tasks such as comprehension of Sequential Commands subtest of the WAB and in word definition. For instance, on defining selected words from the Vocabulary subtest of the WAIS he had up to 5 instances of ME for the same item (see Table 1). When ASL was asked to define the word "impede", he responded: "impede? imposition, impede... impede elements of... no, elements no! impede is to construct, no construct but... impede elements, situations, impede situations".⁴ He also showed frequent perseverations, especially in the picture description (Picnic Scene) of the WAB. He seemed to be partially aware of his RVB.

⁴ Examples were selected based on the similarity of the Spanish and English word to facilitate translation.

Subject 3: *Conduite d'approche and mitigated echolalia*

The subject, MFM, was a 51-year-old right-handed man who suffered a hemorrhagic stroke affecting the left fronto-temporo-parietal region. Before the stroke, he worked as a police inspector. He was referred to our unit 8 months after aphasia onset. At that time, his Aphasia Quotient score was 61.9 and the language profile was consistent with a Wernicke's aphasia (Table 1) although he also showed features of transcortical sensory aphasia and conduction aphasia. Spontaneous speech was fluent, logorrheic and characterized by word finding difficulties, and semantic perseverations and paraphasias, but there were no phonemic paraphasias or neologisms. Comprehension was moderately impaired, and it was noted that ME mainly occurred in difficult-to-understand sentences from the Yes/No Question subtest of the WAB. Semantic comprehension (Auditory Word Recognition of the WAB) was mildly impaired for body parts, fingers and right-left on his body. For some items, when MFM was unable to recognize the name of such auditory-presented words, he could rapidly recognize their meaning once the word was written by the examiner (word-meaning deafness - Bormann & Weiller, 2012; Franklin, Turner, Ralph, Morris, & Bailey, 1996; Kohn & Friedman, 1986). Performance on repetition was differently affected depending on the stimulus. Repetition of single words was preserved, nonword repetition was mildly impaired, and sentence repetition was severely impaired. In the repetition subtest of the WAB he could repeat correctly 6/7 words and only 3/8 short phrases. These findings suggest a mixed profile with deficits in both phonological processing and meaning access. MFM also had difficulties retrieving names (anomia). Additionally, he showed short-term memory deficits with a forward digit span of 3–4. He seemed to be aware of his aphasic deficits.

It is remarkable that language evaluation in MFM displayed key features of three different types of fluent aphasias and, in consonance with it, his speech was punctuated by several instances of automatic echolalia, ME, and CdA. MFM presented automatic echolalia for single words when he was asked to point to real objects and pictures of the Auditory Word Recognition subtest of the WAB. The occurrence of ME was also frequent in tasks requiring meaning access, especially in the Yes/No Questions subtest of the WAB, Auditory Lexical Decision (EPLA 5) and word definition (WAIS). In the former task, for example, the question: "Do you live in Madrid?" (Question 5) elicited "No, not in Madrid", a response that incorporated part of the question, a typical feature of ME. In the same vein, MFM also produced ME in the form of paraphrases of the target sentence. The question "Is a horse larger than a dog?" (Question 19) was echoed as "The horse runs more, it is larger!!". Instances of ME were also heard in tasks that required discrimination of phonological structure. In the Auditory Lexical Decision task (EPLA 5) MFM repeated the heard stimulus several times because he was not sure whether it was a real word or not. Finally, on defining a "mountain", he said: "to the mountain you go... is the mountain, is at the sea, no! How did you say? there, up... The sea is down and the mountain up". Interestingly, besides ME he also showed several instances of CdA, mainly while performing naming tasks. Sometimes, these phonemic approximations led to the correct response (e.g., target noun: "giraffe"; MFM's response: "giraba... girasa... gira... giraffe!"), while other corrective attempts were unsuccessful.⁵ In some occasions, CdA led to semantic or phonemic paraphasias. He seemed partially aware of these behaviors.

3.2. Neuroimaging results: Lesion location, lesion-based disconnection analysis and metabolic findings

Subject 1: *Conduite d' approche*

⁵ Instances of unsuccessful conduite d'approche were difficult to translate into English (e.g. for the Spanish target noun "martillo" (Spanish word for hammer), patient responded: mar, marti, martido!).

The structural T₁-weighted image in AFR showed a large lesion affecting the left middle and superior temporal gyri including the gyrus of Heschl, the inferior parietal cortex (angular and supramarginal gyri), a small part of the posterior insula and the underlying white matter (Figs. 1A and 2A). As outlined above, a lesion-based disconnection analysis using Tractotron software was used to explore the probability of a given tract of being directly affected by the lesion as well as the percentage of each tract directly affected by the injury. Results revealed that, for the dorsal language pathways, the long and the posterior AF segments were affected with a probability of 100%, while the anterior AF showed a probability 98%. Regarding the ventral pathways, a 100% probability of damage was found for the IFOF, the ILF and the UF. The fact that all the ventral and dorsal studied white matter tracts were affected was not surprising given the extension of the lesion (Figs. 1 and 2A). However, the probability of each tract to be damaged is not a very informative measure itself. A more comprehensive picture can be provided by the lesion load index (i.e., a measure indicating the proportion of each tract directly compromised by the lesion), and by the specific part of the track affected. In this subject, the lesion load analysis indicated that the lesion directly affected the 18.5% of the anterior AF, 56% of the long AF and 72.1% of the posterior AF segments. With respect to the ventral pathways, 6.8% of the IFOF, 6% of the ILF and 2.3% of the UF were affected. Fig. 2A depicts the overlap between the lesion mask (pink color) and both the dorsal and the ventral pathways as well as the average percentage of damage for each group of tracts, showing greater lesion load in the dorsal ones. Further, Disconnectome map revealed distant regions, not directly affected by the lesion, showing high probability of being disconnected (> 90%) from other areas, including the inferior temporal gyrus, insula, inferior frontal gyrus and the thalamus (Fig. 2A).

Finally, PET analysis showed regions of significantly decreased metabolic activity in areas of the left hemisphere surrounding the lesion (see Table 2 and Fig. 3A), comprising the perilesional middle temporal gyrus, the planum temporale in the superior temporal gyrus, the insula and the angular gyrus. No significant metabolic increases were found in the left hemisphere. The right hemisphere showed normal metabolic activity compared to controls.

Subject 2: *Mitigated Echolalia*

The structural MRI in ASL showed small multifocal traumatic lesions involving posterior regions of the left hemisphere including the inferior temporal, the fusiform and the lingual gyri, the inferior parietal cortex and the thalamus (Fig. 1B). Regarding the white matter pathways directly affected by the lesion, the three studied segments of the AF showed high probability of being damaged: 96% for the anterior AF, 96% for the long AF and 98% for the posterior AF. Considering the ventral pathways, the IFOF had a probability of 92% of being affected, 100% in the case of the ILF and 0% in the case of the UF. Lesion load analysis showed that the anterior AF was affected in a 0.8%, the long AF in a 1.7%, and the posterior AF in a 0.7%. The ventral pathways showed also a low lesion load, where 0.4% of the IFOF was damaged, 2.5% of the ILF and the 0% of the UF (Fig. 2B). However although the lesion load in ventral pathways was low, the location of the lesion bisected this pathway discontinuing the projection of fibers that run through it, as seen in the Disconnectome map figure (see Fig. 2B, red color). This was not the case for the dorsal pathways, where the amount of fibers was certainty diminished in its caudal part, but the lesion did not preclude transmission through it.

Different distant regions were found to have a high probability of being affected due to their connectivity with the injured areas, specifically: extended parts of the inferior and middle temporal gyri, the parietal and premotor cortices and the orbital and inferior frontal gyri (pars triangularis) (Fig. 2B). Crucially, PET analysis revealed different clusters with significant decrements of metabolic activity in different areas of the left hemisphere, including the middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, supramarginal and angular gyri in the inferior parietal cortices, parahippocampal gyrus and precuneus.

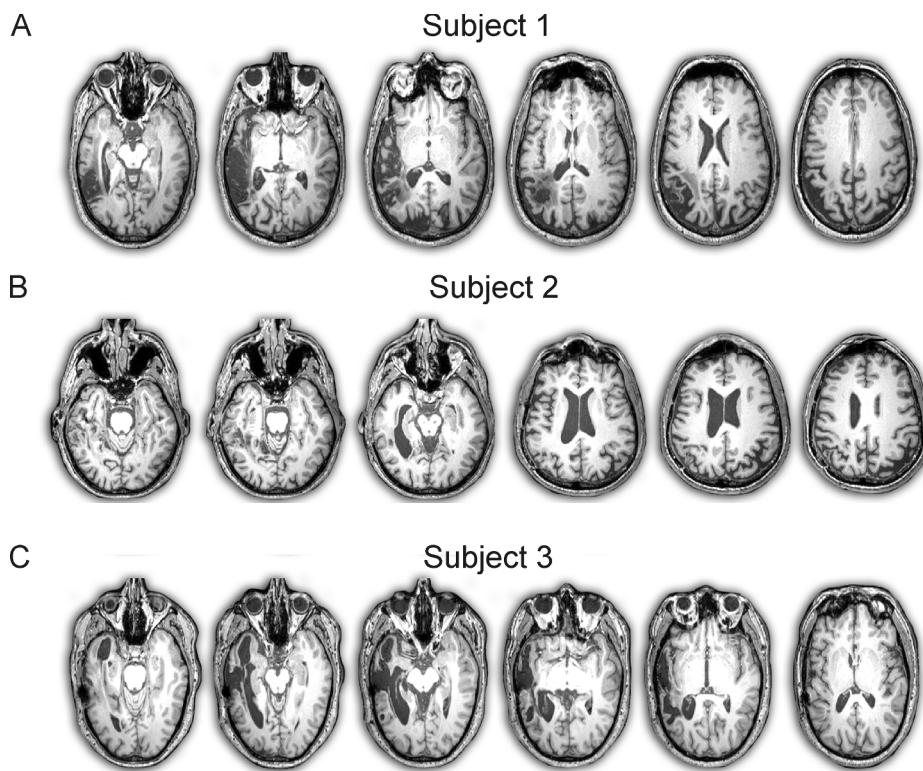


Fig. 1. T₁-weighted MRI axial images depicting left hemisphere brain damage in the three subjects in native space. Images are shown in neurological convention. Subject 1 had a large area of cortical damage in the temporal, insular and inferior parietal regions with subcortical extension into the temporo-parietal white matter. Subject 2 had several small traumatic foci scattered to the left inferior temporal cortex and parahippocampal gyrus together with a moderate dilatation of the ipsilateral temporal horn of the lateral ventricle. Subject 3 had a large lesion involving the left temporal pole extending posteriorly to affect great parts of the middle and superior temporal gyri. He also had moderate dilatation of the left temporal horn of the lateral ventricle. None of the subjects showed lesions in the right hemisphere.

Furthermore, a focus of increased metabolism was found in a deep parietal region of the right hemisphere, corresponding with the place in which the long and the anterior AF segments run in their way from the frontal to the temporal and parietal cortices (Table 2 and Fig. 3B). This data suggests compensation of ventral damage through dorsal pathways, probably bilaterally.

Subject 3: *Conduite d'approche and mitigated echolalia*

The structural MRI in MFM showed a lesion comprising the left superior temporal pole, the middle temporal gyrus, the anterior part of the superior temporal gyrus and the medial portion of the inferior temporal gyrus with sparing of the primary auditory areas in the superior temporal gyrus (Figs. 1C and 2C). Regarding the direct effect of the lesion on white matter, Tractotron revealed a high probability of damage for all studied dorsal pathways: 82% for the anterior AF, 98% for the long AF and 100% for the posterior AF. Considering the ventral tracts, a 100% probability of affection was found for the IFOF and ILF and a 98% for the UF. When the lesion load in each fasciculus was analyzed, we found that a 0.05% of the anterior AF, 13.4% of the long AF, and 17.2% of the posterior AF were affected. For the ventral pathways, it was found that a 1.3% of the IFOF, 7.2% of the ILF, and 13.7% of the UF were affected (Fig. 2C).

Disconnectome map analysis revealed that the lesion affected with a high probability (> 90%) the connectivity to distant areas in the left hemisphere such as the middle temporal gyrus, the superior temporal gyrus, the inferior parietal cortex, the posterior insula, the orbital cortex and the thalamus (Fig. 2C). PET analysis revealed decreased glucose metabolism in the whole inferior temporal gyrus, in perilesional areas such as the middle temporal gyrus and in some small areas in the superior temporal gyrus and the angular gyrus. No significant metabolic increases in the left hemisphere were found (Fig. 3C). Metabolic activity in the right hemisphere was preserved.

4. Discussion

We described the occurrence of CdA, ME and both RVBs in three subjects with fluent aphasias. Although these RVBs are not rare, the

neural networks that support their occurrence after brain damage have not been fully investigated yet. Thus, contrary to what occurs in residual language deficits (e.g. reduced auditory comprehension due to non-functional brain tissue), RVBs cannot emanate from a fully dysfunctional brain network. Thereby, we reasoned that these behaviors cannot be explained by the direct effect of the lesion. Rather, their occurrence may reflect compensatory changes aiming to overcome residual language deficits caused by the injury, relying on preserved language-related networks. With this idea in mind, the aim of the present study was to examine the clinical features and neural basis of isolated or concurrent CdA and ME in three subjects with different types of fluent aphasias. These index cases exemplify how the brain can adjust its residual function to produce RVBs. We used multimodal imaging to (i) disentangle the cortical areas and white matter tracts affected in the three subjects showing these RVBs; and to (ii) identify which spared cortical areas and white matter tracts may be involved in the expression of these RVBs.

A relevant finding of our study was that each type of RVB could be related to a relatively different neural signature with respect to the language pathway involved. Comparatively, the subject with CdA (AFR) had more dorsal involvement, the subject with ME (ASL) had a more ventral affection, whereas the subject showing both types of symptoms (MFM) had affection of both white matter pathways with a pattern in between the other two cases (Fig. 4). These findings fit well with the results of preliminary studies in which CdA has been associated to damage of the dorsal pathway (Ueno & Lambon Ralph, 2013) and ME with ventral stream injury (Berthier, Torres-Prioris et al., 2018). However, the neural signatures of combined CdA and ME have not been explored so far.

Subject 1 (AFR) presented a *reproduction* CA with phonemic paraphasias in all production tasks, mildly impaired comprehension mainly for body parts and long sentences, severely impaired repetition of nonwords and sentences, and mildly impaired picture naming. He also presented instances of CdA in several production tasks (repetition, naming, and word definition) associated to a large left temporo-parietal and posterior insular infarct. Structural MRI and PET data for this

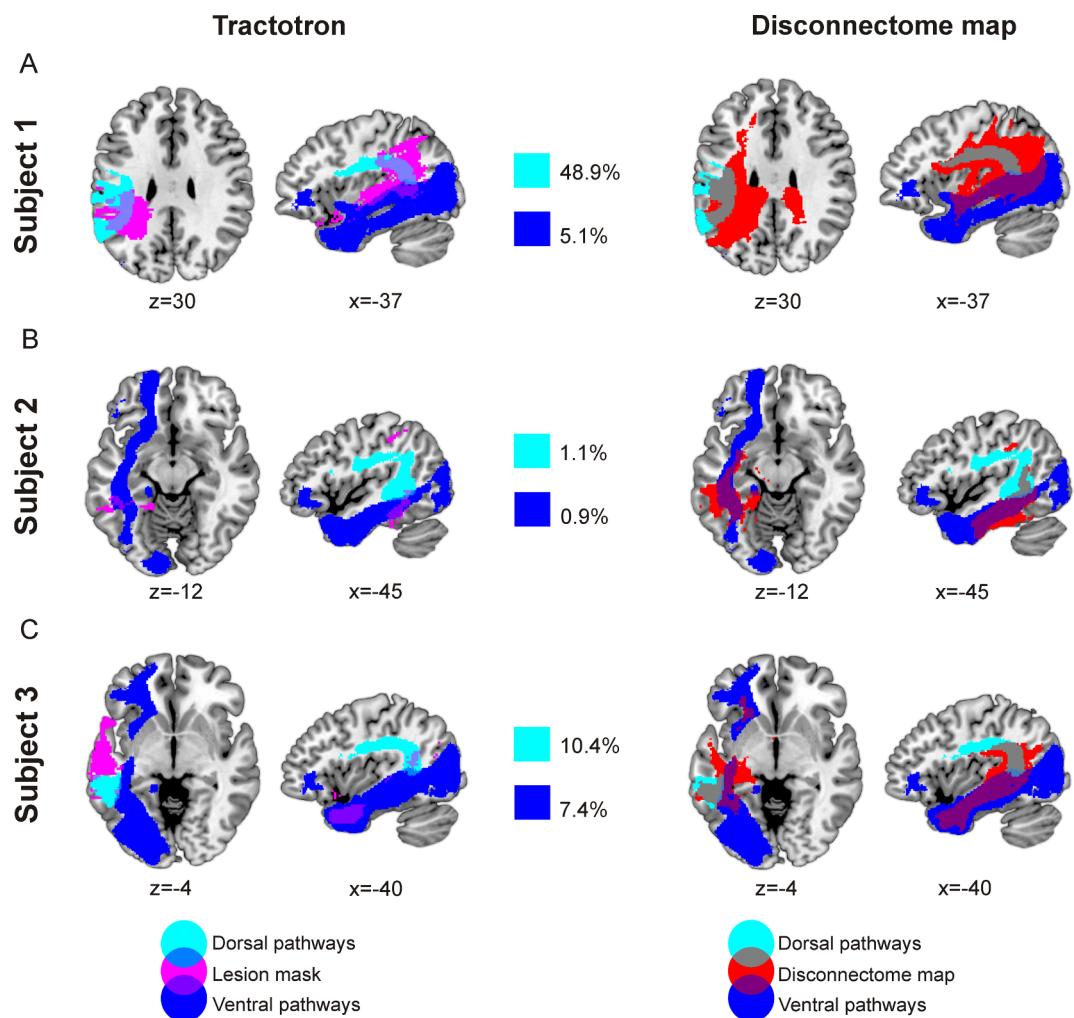


Fig. 2. Lesion-based disconnection analysis. The left column shows the overlap between each subject's lesion mask (pink) and both the dorsal (sum of the long, anterior and posterior segments of the arcuate fasciculus [AF], light blue) and the ventral (sum of the inferior fronto-occipital fasciculus [IFOF], inferior longitudinal fasciculus [ILF] and uncinate fasciculus [UF], dark blue) white matter templates. The percentage of damage for the ventral (average between the ILF, IFOF and UF percentages) and the dorsal (average between the anterior AF, posterior AF and long AF percentages) pathways are shown, as calculated with the Tractotron software. The right column shows the overlap between each subject's disconnectome map (red) and the same dorsal and ventral templates. Probabilistic templates for the dorsal and the ventral tracts were extracted from Tractotron white matter atlas from healthy subjects (<http://toolkit.bcbilab.com>) and were thresholded at 70%. The normalized templates of white matter tracts, the lesions masks and the disconnectome maps were superimposed onto a T1-weighted image in MNI provided by MRIcron software.

subject indicated that, with a high probability, the lesion compromised both language streams. However, the dorsal stream showed higher disconnection (higher percentage of the track compromised by the lesion: 48.9%, Fig. 2A), than the ventral pathway, which although affected, was not severely disconnected (5.1%, Fig. 2A). Moreover, PET analysis showed reduced metabolic activity in perilesional areas sparing regions corresponding to the ventral stream. Our findings concur with those from computational modeling (Ueno & Lambon Ralph, 2013) and studies of patients with brain lesions (Berthier et al., 2013; Berthier, Torres-Prioris et al., 2018; Rauschecker et al., 2009; Yeatman & Feldman, 2013) and healthy subjects (Lopez-Barroso et al., 2011). Altogether, these data suggest that CdA may emerge from the compensatory activity of the spared left ventral stream in an attempt to overcome residual deficits in language processing (comprehension, repetition and naming). For instance, during the administration of the sentence repetition subtest of the WAB, Subject 1 occasionally showed a “lexical bias” with production of semantic paraphasias (e.g., “ringing” → “calling”) when he forgot or was unable to repeat the last words verbatim, reflecting involving of the ventral stream (McKinnon et al., 2017). Although metabolic activity of the right hemisphere in this

subject did not differ from data obtained from a healthy control group, we do not discard the contribution of the homologous right dorsal and ventral streams to the observed RVB.

Subject 2 (ASL) had a transcortical sensory aphasia with anomia and perseverative speech production, impaired verbal comprehension and naming in the face of an almost intact repetition with echolalia. He presented automatic echolalia only for single words, but ME was more abundant and it was produced in demanding comprehension tasks. Consistent with previous descriptions of the neural basis of transcortical sensory aphasia (Rubens & Kertesz, 1983, chap. 10), neuroimaging in ASL disclosed multiple confluent lesions scattered throughout the left posterior-inferior temporal lobe. PET analysis showed reduced metabolic activity in posterior areas through which travels the left ventral stream. Moreover, a cluster of significant increased metabolic activity was found in the right white matter corresponding with the anterior and the long segments of the AF. In the left hemisphere, the anterior AF segment has been related to phonological working memory (Papagno et al., 2017) and verbal fluency (Fridriksson et al., 2013), whereas the long AF segment was related to verbal repetition (Saur et al., 2008). Importantly, although the proportion of the ventral pathways affected

Table 2

Whole brain Positron Emission Tomography (PET) results. Brain areas with decreased hypometabolic and increased hypermetabolic metabolic activity in the three aphasic subjects relative to 24 healthy control subjects.

p FWE-corrected	t-value	Peak coordinates*			Cluster size	Regions (n voxels)***
		x	y	z		
<i>Subject 1</i>						
– 0.000	12.68	–48	–40	46	48	L inferior parietal cortex
0.000	10.74	–42	–16	–10	124	L insula, L hippocampus, L superior temporal, L middle temporal gyrus
0.000	10.17	–42	–24	12	46	L rolandic operculum, L insula, L Heschl gyrus, L superior temporal gyrus
0.000	9.74	–56	–34	38	15	L inferior parietal cortex, L supramarginal gyrus
0.014	7.05	–20	–30	10	15	L hippocampus, L thalamus
<i>Subject 2</i>						
– 0	12.23	–24	–48	–12	2934	L posterior cingulum, L hippocampus, L parahippocampal, L calcarine sulcus, L lingual gyrus, L middle occipital gyrus, L inferior occipital cortex, L fusiform gyrus, Postcentral L, L inferior parietal, L supramarginal gyrus, L angular gyrus, L precuneus, L thalamus, L middle temporal, L inferior temporal, L cerebellum, Sub-gyral (involving White matter corresponding to the AF)
<i>Subject 3</i>						
– 0	21.36	–56	–44	4	3861	L hippocampus, L parahippocampal gyrus, Occipital Middle L, L inferior occipital gyrus, L fusiform gyrus, L angular gyrus, L superior temporal gyrus, L superior temporal, L middle temporal gyrus, L middle temporal pole, L inferior temporal gyrus, L Cerebellum
0.011	7.18	–18	58	0	29	L lingual gyrus
0.02	6.84	–16	–82	–14	18	L Cerebellum
0.031	6.62	–8	–92	–2	10	L calcarine sulcus

* Peak coordinates represent the location of the maximum pixel value in standard Montreal Neurological Institute (MNI) space.

** Threshold of 10 voxels applied.

*** From all MNI V4 atlases included in the WFU Pickatlas toolbox (R = Right, L = Left). –: Indicates decreased metabolic activity in comparison to healthy controls. +: indicates increased metabolic activity.

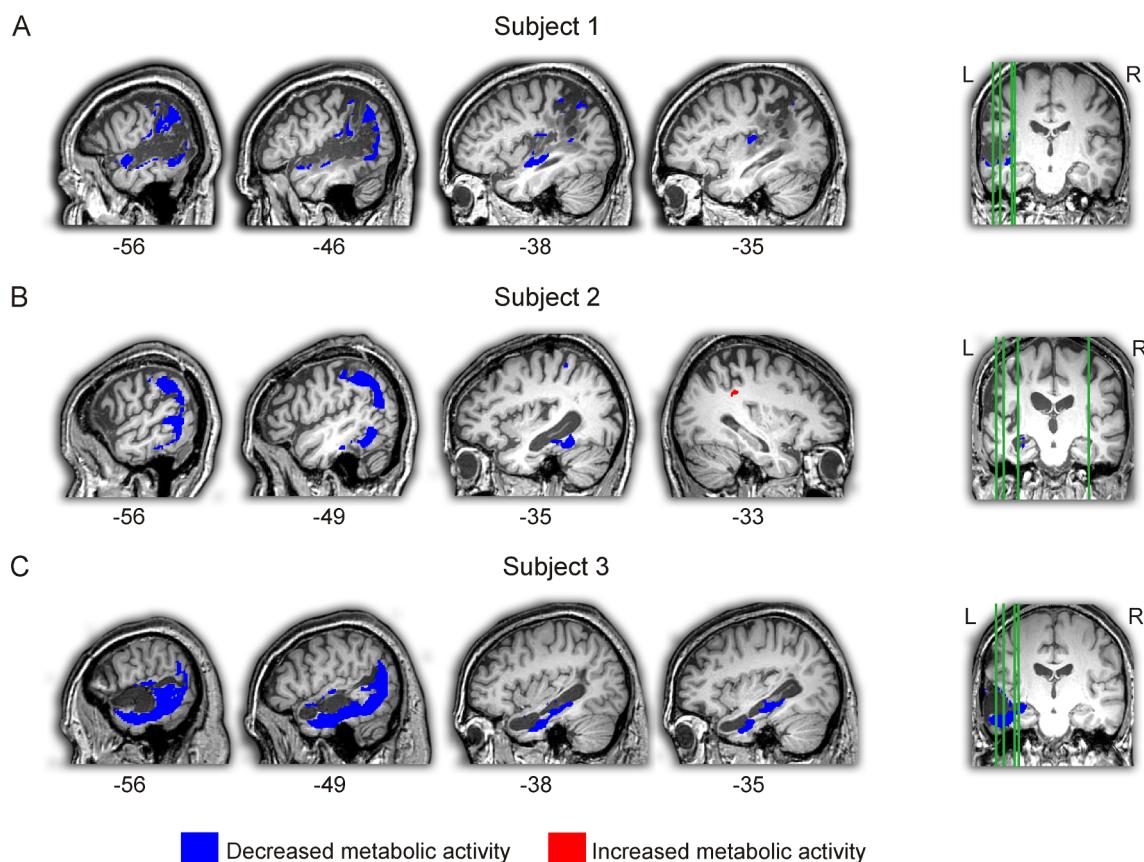


Fig. 3. [18F]-FDG-PET shows areas of hypometabolism and hypermetabolism in the three subjects. Parasagittal PET images show significant reductions of metabolic activity (hypometabolism) mostly in perilesional areas of the left hemisphere. Only subject 2 showed a cluster of significant increased metabolic activity (hypermetabolism) in the right hemisphere. This metabolic increase was in a region in which the white matter of the anterior and the long segments of the arcuate fasciculus crosses, possibly reflecting compensatory plastic mechanisms. A statistic threshold of $p < 0.05$ (FWE corrected) was applied.

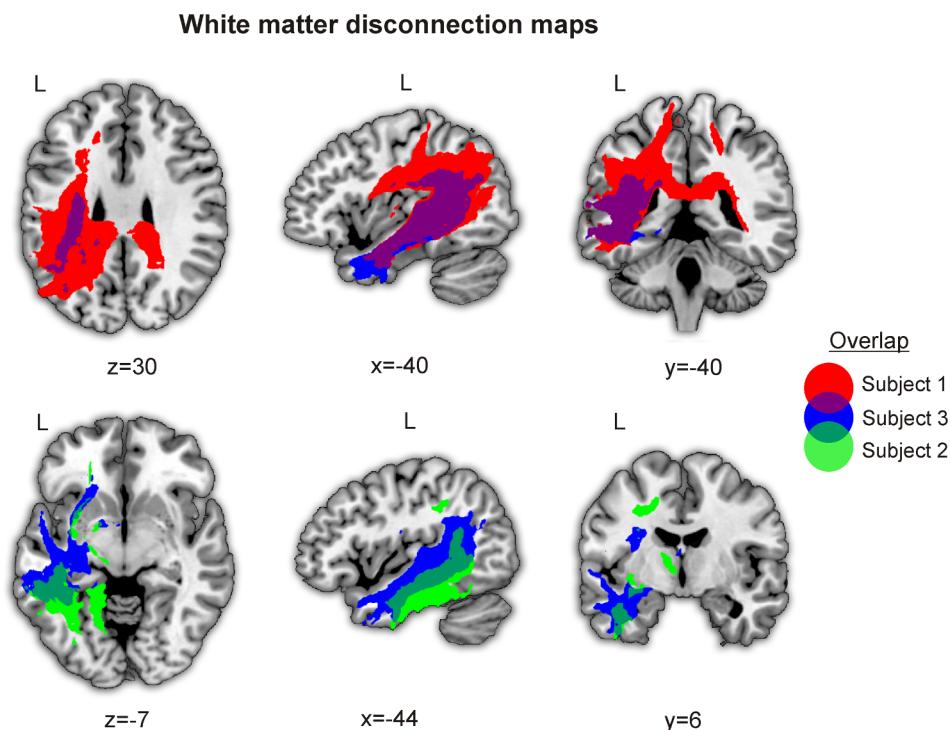


Fig. 4. Disconnectome maps of the three subjects. Each map depicts the areas that, although not directly affected by the lesion, show a probability of disconnection equal or > 90%. Subject 1 with conduction aphasia and instances of conduite d'approche (CdA), shows higher probability (red) of having dorsal regions disconnected, whereas subject 2 (green), with transcortical sensory aphasia and frequent instances of mitigated echolalia (ME), shows higher probabilities of disconnection of ventral areas. Subject 3, with Wernicke's aphasia and instances of both RVBs (CdA and ME) has disconnection of both, ventral and dorsal areas.

was relatively low (low lesion load: < 1%), the confluence of several small lesions in the trajectory of this tract may be ideally suited to induce a complete disconnection (Hope et al., 2016). Thus, based on these results we suggest that ME in ASL resulted from compensatory activity of the spared dorsal stream and, possibly, from the vicarious activity of the right hemisphere. In line with our results, a relationship between compensatory activity in the preserved right hemisphere and ME has been found in a case of chronic residual Wernicke's aphasia associated with damage to the left ventral stream (Berthier, Torres-Prioris et al., 2018). In the case of ASL, compensatory plastic changes may have emerged in an attempt to compensate for the comprehension and naming deficits. Note that repeating over and over a word or a short sentence that cannot be understood may increase the chance of meaning access (Hickok et al., 2011).

Finally, according to the WAB taxonomic criteria (Kertesz, 1982) Subject 3 (MFM) showed a language disturbance consistent with a Wernicke's aphasia associated with extensive damage to the left temporal lobe. However, phonemic paraphasias and neologisms in running speech, typical of Wernicke's aphasia, were conspicuously absent. His spontaneous speech was anomia resembling transcortical sensory aphasia and although repetition was mildly impaired, he had instances of automatic echolalia and ME characteristic of transcortical aphasias (Berthier, Dávila, & et al., 2018). Lastly, phonemic approximations (CdA), characteristic of conduction aphasia, were mostly heard in naming tasks (Nadeau, 2001). A similar case describing the co-occurrence or alternation of these RVBs occurred in a subject with conduction aphasia who showed instances of CdA of echoed words (Brown, 1975). Structural MRI and PET imaging in MFM showed that ME and CdA were associated with involvement of areas overlapping with the lesions described in the other two subjects, compromising components of both the dorsal and ventral streams (Fig. 4). Therefore, this kind of behavior in Subject 3 might reflect instability in the underlying networks with iterative network alternation aimed to comply with the function required.

The presence of these two RVBs in PWA implies the possibility of producing either speech errors or instances of fully accurate verbal behavior, which may depend upon brain remodeling that dynamically modifies the interaction between dysfunctional areas and intact brain

tissue (Hylin, Kerr, & Holden, 2017; Welbourne, Woollams, Crisp, & Lambon Ralph, 2011). Neural compensation after brain injury results from plastic mechanisms involving the recruitment of alternative white matter pathways to communicate nearby or distant brain regions, or the recruitment of different cortical areas. The unstable activity of these white matter tracts and the cortical areas they link is usually associated to the production of errors (i.e., semantic paraphasias during word list repetition) (see case JVA in Berthier, Lambon Ralph, Pujol, & Green, 2012) or to suboptimal, yet adaptive, behavioral achievements. Thus, RVBs might occur because the activity of newly recruited areas is not sufficiently stable or efficient to fully mimic the activity of areas originally devoted to a given language function (Lee et al., 2017; Postman-Caucheteux et al., 2010). Therefore, a tenable interpretation would be that the production of speech errors, like CdA and ME, are not totally linked to structural and functional damage, but result from a yet fragile and unstable compensation by undamaged brain areas.

Brain language networks dynamically interact to achieve optimal verbal outcomes (Cloutman, 2013; Fridriksson et al., 2016; Gierhan, 2013). In an undamaged brain, normal verbal behavior (Hickok & Poeppel, 2007) can be subserved by: (i) a network with bilateral well-developed dorsal and ventral tracts (Fig. 5A and 5B); or (ii) a network with well-developed dorsal tracts in the left hemisphere (left-lateralized) (Fig. 5A) but vestigial direct segment of the dorsal pathway in the right hemisphere (Fig. 5C), together with a fully developed ventral stream in both hemispheres (Catani & Bambini, 2014; Catani et al., 2005). However, alternative pathways may be used to support verbal behavior after brain injury. Fig. 5D depicts a hypothetical brain reorganization in which compensatory activity may likely result in CdA due to damage to the left dorsal pathway with sparing of the ipsilateral ventral one, as suggested by Rijntjes et al. (2012) and Ueno and Lambon Ralph (2013) as well as by data from subject 1 in the present study. Note, however, that more severe cases of reproduction or output conduction aphasia showing CdA (Gvion & Friedmann, 2012; Nadeau, 2001; Shallice & Warrington, 1977) often result from large lesions that involve both the left dorsal and ventral streams (Fig. 5E) (Axer, v. Keyserlingk, Berks, & v. Keyserlingk, 2001; Pate, Saffran, & Martin, 1987; Rosso et al., 2015). This scenario would imply that CdA not always results from the activity of the left ventral stream. Therefore, we

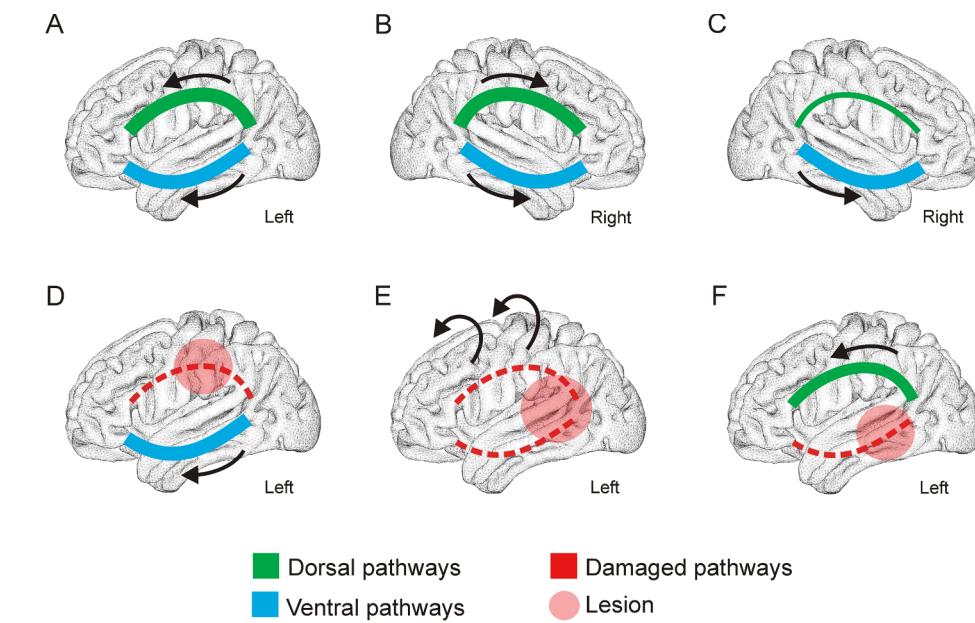
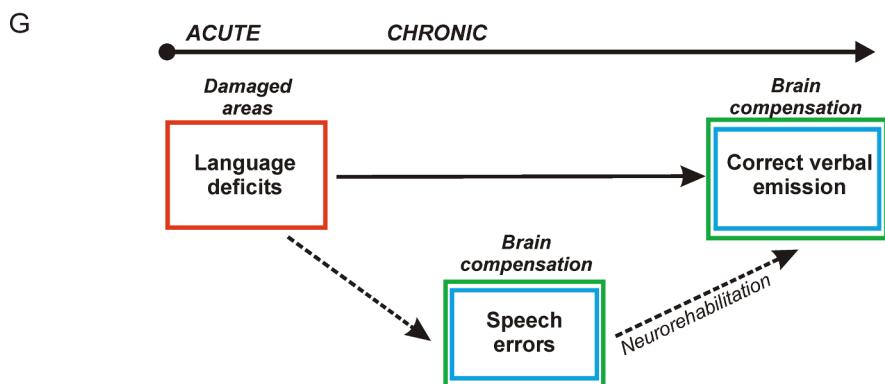


Fig. 5. A-F. Illustration of different possible patterns of preserved and damaged dorsal and ventral white matter pathways implicated in repetitive verbal behaviors. Tracts were superimposed on a 3D rendering of a T₁-weighted MRI from a healthy subject. For illustrative purposes, the ventral and the dorsal tracts are represented with a blue and a green line, respectively. Thick lines represent an intact tract, whereas thin lines reflect an undeveloped tract. Tracts depicted in blue and green represent undamaged tracts; damaged pathways are represented in red; and the black arrows point to the preferential route for language processing depending upon the tracts availability. G. Schematic representation of the proposed evolution of aphasic symptoms. Notice that colors of the boxes represent the underlying damaged and undamaged tracts depicted in panels A-F.



have delineated simultaneous damage of both left dorsal and ventral streams envisioning that in this circumstance CdA could be supported by the compensatory activity of right white matter pathways (Fig. 5B or C). In the same line, damage to the left ventral stream with totally or partially sparing of the dorsal pathway may result in ME (Fig. 5F). These patterns are supported by data from subjects 2 and 3 in the present study. Alternatively, if damage to both pathways in the left hemisphere induces ME (Fig. 5E), this RVB may emerge from the activity of right white matter tracts (Fig. 5B or C) as it may also occur for CdA. Functional and anatomical differences in the right hemisphere (e.g., volume of the direct segment of the AF) and the network that previously sustained a specific function may play a role in the clinical outcome after damage to the language system (Forkel et al., 2014). Further studies are needed to identify the variables implicated. Finally, it is also possible that other preserved pathways, such as the frontal aslant tract in the left hemisphere might play a role in ME (López-Barroso & de Diego-Balaguer, 2017). The role of short association U-fibers connecting cortical regions between adjacent gyri should not be dismissed until further studies are performed.

As a final note, it is worth mentioning that additionally to the structural MRI and PET, we used two complementary lesion-based analyses (one tract-specific and one data-driven) to further explore the local and remote effects of the lesion at a structural level. The Tractotron represents an atlas-based analysis of disconnection that

permits to identify tracts that could be directly affected by the lesion and the direct lesion load; whereas Disconnectome map is a data-driven analysis that results in individual maps of disconnection that also consider the distant effect of the lesion based on its localization and extension. In our three subjects, Tractotron revealed either a high direct lesion load or damage in a crucial part of the dorsal and ventral tracts, causing disconnection. This confirmed that the two RVBs studied here arise with high probability from the more preserved pathway in each case (Fig. 2A). Furthermore, Disconnectome maps graphically revealed the lesion-based disconnection pattern for each subject. This allowed the comparison of the three disconnection maps, providing additional evidence showing that the dorsal or ventral areas indirectly affected by the injury vary among the three subjects according to the expressed RVB. However, further studies that provide a careful evaluation of these RVBs in larger samples are needed. Thus, these studies could correlate the severity of the disconnection (or lesion load, as revealed by Tractotron) or the individual disconnection maps with behavioral data, following the same logic as the one behind the voxel-based lesion-symptom mapping, but focused on tract disconnection.

In conclusion, we argue that the study of RVBs, like CdA and ME, in aphasia can inform how intact components of a damaged brain are engaged to readjust the activity of cortical tissue and white matter tracts to compensate the deleterious effect of brain lesions. This is important not only from a theoretical perspective, but also to inform the

development of model-based therapeutic interventions aimed to enhance optimal plastic changes within the network mediating these verbal behaviors (see Fridriksson et al., 2012; Sarasso et al., 2014). After acute brain injury, tissue damage makes directly evident the appearance of residual language deficits (e.g., mutism, nil comprehension) (Fig. 5G). Later in the chronic stage, although subjected to huge individual variability, residual language deficits normally evolve to either accurate verbal emissions or to speech errors (i.e., an attempt to communicate or comprehend language) (Fig. 5G). We contend that the presence of RVBs, specifically CdA and ME, can be viewed as a therapeutic opportunity since they represent an active, yet suboptimal, attempt to improve communication rather than as symptoms to be eradicated (Berthier et al., 2017). Therefore, the role of therapies aimed to redirect, modulate and optimize these symptoms to reach accurate verbal behavior (Fig. 5G) should be evaluated in future research.

5. Statement of significance

Conduite d'approche and mitigated echolalia are produced to overcome phonological and lexico-semantic deficits, respectively. CdA reflects compensatory activity of the ventral (semantic) language pathway when the dorsal (phonological) pathway is damaged, whereas ME reflects the compensatory function of the dorsal pathway after damage to the ventral route.

Funding

MJTP and JPP have been funded by PhD scholarships from the Spanish Ministry of Education, Culture and Sport under the FPU program (MJTP: FPU14/04021; JPP: FPU16/05108). DLB has been supported by a postdoctoral grant from the University of Malaga.

References

- Albert, M. L., Goodglass, H., Helm, N. A., Rubens, A. B., & Alexander, M. P. (1981). *Clinical Aspects of Dysphasia*. Vienna: Springer.
- Axer, H., v. Keyserlingk, A. G., Berks, G., & v. Keyserlingk, D. G. (2001). Supra- and Infrasylvian Conduction Aphasia. *Brain and Language*, 76(3), 317–331. <https://doi.org/10.1006/BRLN.2000.2425>.
- Baldo, J. V., Klostermann, E. C., & Dronkers, N. F. (2008). It's either a cook or a baker: Patients with conduction aphasia get the gist but lose the trace. *Brain and Language*, 105(2), 134–140. <https://doi.org/10.1016/J.BANDL.2007.12.007>.
- Basilakos, A., Fillmore, P. T., Rorden, C., Guo, D., Bonilha, L., & Fridriksson, J. (2014). Regional white matter damage predicts speech fluency in chronic post-stroke aphasia. *Frontiers in Human Neuroscience*, 8, 845. <https://doi.org/10.3389/fnhum.2014.00845>.
- Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience*, 6(5), 448. <https://doi.org/10.1038/nn1050>.
- Berthier, M. L., Dávila, G., & Torres-Prioris, M. J. (2018). Echophenomena in aphasia: Causal mechanisms and clues for intervention. In P. Coppens, J. Patterson (Eds.), *Aphasia Rehabilitation: Clinical Challenges*, Burlington, MA: Jones & Bartlett Learning (pp. 143–172).
- Berthier, M. L., Froudist Walsh, S., Dávila, G., Nabrozhid, A., Juárez, Y., Ruiz de Mier, R., ... García-Casares, N. (2013). Dissociated repetition deficits in aphasia can reflect flexible interactions between left dorsal and ventral streams and gender-dimorphic architecture of the right dorsal stream. *Frontiers in Human Neuroscience*, 7, 873. <https://doi.org/10.3389/fnhum.2013.00873>.
- Berthier, M. L., Lambon Ralph, M. A., Pujol, J., & Green, C. (2012). Arcuate fasciculus variability and repetition: The left sometimes can be right. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 48(2), 133–143. <https://doi.org/10.1016/j.cortex.2011.06.014>.
- 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. <https://doi.org/10.3389/fnhum.2017.00164>.
- 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. <https://doi.org/10.1080/02687038.2016.1274875>.
- Bormann, T., & Weiller, C. (2012). Are there lexicons? A study of lexical and semantic processing in word-meaning deafness suggests "yes". *Cortex*, 48(3), 294–307. <https://doi.org/10.1016/J.CORTEX.2011.06.003>.
- Brauer, J., Anwander, A., & Friederici, A. D. (2011). Neuroanatomical prerequisites for language functions in the maturing brain. *Cerebral Cortex*, 21(2), 459–466. <https://doi.org/10.1093/cercor/bhq108>.
- Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *NeuroImage*, 14(2), 486–500. <https://doi.org/10.1006/NIMG.2001.0845>.
- Brown, J. W. (1975). The problem of repetition: A study of "Conduction" aphasia and the "Isolation" syndrome. *Cortex*, 11(1), 37–52. [https://doi.org/10.1016/S0010-9452\(75\)80019-0](https://doi.org/10.1016/S0010-9452(75)80019-0).
- Catani, M., & Bambini, V. (2014). A model for Social Communication And Language Evolution and Development (SCALeD). *Current Opinion in Neurobiology*, 28, 165–171. <https://doi.org/10.1016/J.CONB.2014.07.018>.
- Catani, M., Jones, D. K., & Ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology*, 57(1), 8–16. <https://doi.org/10.1002/ana.20319>.
- Catani, M., & Mesulam, M. (2008). The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 44(8), 953–961. <https://doi.org/10.1016/j.cortex.2008.04.002>.
- Christman, S. S., Boutsen, F. R., & Buckingham, H. W. (2004). Perseveration and other repetitive verbal behaviors: Functional dissociations. *Seminars in Speech and Language*, 25(04), 295–307. <https://doi.org/10.1055/s-2004-837243>.
- Cloutman, L. L. (2013). Interaction between dorsal and ventral processing streams: Where, when and how? *Brain and Language*, 127(2), 251–263. <https://doi.org/10.1016/J.BANDL.2012.08.003>.
- Damasio, A. R., & Damasio, H. (1992). Brain and language. *Scientific American*, 267(3), 88–109.
- Dell, G. S., Schwartz, M. F., Nozari, N., Faseyitan, O., & Branch Coslett, H. (2013). Voxel-based lesion-parameter mapping: Identifying the neural correlates of a computational model of word production. *Cognition*, 128(3), 380–396. <https://doi.org/10.1016/J.COGNITION.2013.05.007>.
- Druks, J., & Masterson, J. (2000). *Object and action naming battery*. Psychology Press.
- Fisher, W., Burd, L., & Kerbeshian, J. (2008). Markers for improvement in children with pervasive developmental disorders. *Journal of Intellectual Disability Research*, 32(5), 357–369. <https://doi.org/10.1111/j.1365-2788.1988.tb01426.x>.
- Forkel, S. J., Thiebaut de Schotten, M., Dell'Acqua, F., Kalra, L., Murphy, D. G. M., Williams, S. C. R., & Catani, M. (2014). Anatomical predictors of aphasia recovery: A tractography study of bilateral perisylvian language networks. *Brain*, 137(7), 2027–2039. <https://doi.org/10.1093/brain/awu113>.
- Foulon, C., Cerliani, L., Kinkingnæhun, S., Levy, R., Rosso, C., Urbanski, M., ... Thiebaut de Schotten, M. (2018). Advanced lesion symptom mapping analyses and implementation as BCBCtoolkit. *GigaScience* 7(3). <https://doi.org/10.1093/gigascience/giy004>.
- Franklin, S., Turner, J., Ralph, M. A. L., Morris, J., & Bailey, P. J. (1996). A distinctive case of word meaning deafness? *Cognitive Neuropsychology*, 13(8), 1139–1162. <https://doi.org/10.1080/0264329963811683>.
- Fridriksson, J., Baker, J. M., & Moser, D. (2009). Cortical mapping of naming errors in aphasia. *Human Brain Mapping*, 30(8), 2487–2498. <https://doi.org/10.1002/hbm.20683>.
- Fridriksson, J., Richardson, J. D., Fillmore, P., Holland, A., & Rorden, C. (2013). Damage to the anterior arcuate fasciculus predicts non-fluent speech production in aphasia. *Brain: A Journal of Neurology*, 136(Pt 11), 3451–3460. <https://doi.org/10.1093/brain/awt267>.
- Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left hemisphere plasticity and aphasia recovery. *NeuroImage*, 60(2), 854–863. <https://doi.org/10.1016/J.NEUROIMAGE.2011.12.057>.
- Fridriksson, J., Yourganov, G., Bonilha, L., Basilakos, A., Den Ouden, D.-B., & Rorden, C. (2016). Revealing the dual streams of speech processing. *Proceedings of the National Academy of Sciences*, 113(52), 15108–15113. <https://doi.org/10.1073/pnas.1614038114>.
- Friederici, A. D. (2012). The cortical language circuit: From auditory perception to sentence comprehension. *Trends in Cognitive Sciences*, 16(5), 262–268. <https://doi.org/10.1016/J.TICS.2012.04.001>.
- Friston, K. J., & Price, C. J. (2003). Degeneracy and redundancy in cognitive anatomy. *Trends in Cognitive Sciences*, 7(4), 151–152.
- Frith, C. D., & Frith, U. (2012). Mechanisms of social cognition. *Annual Review of Psychology*, 63(1), 287–313. <https://doi.org/10.1146/annurev-psych-120710-100449>.
- Geva, S., Correia, M. M., & Warburton, E. A. (2015). Contributions of bilateral white matter to chronic aphasia symptoms as assessed by diffusion tensor MRI. *Brain and Language*, 150, 117–128. <https://doi.org/10.1016/J.BANDL.2015.09.001>.
- Gierhan, S. M. E. (2013). Connections for auditory language in the human brain. *Brain and Language*, 127(2), 205–221. <https://doi.org/10.1016/J.BANDL.2012.11.002>.
- Gleichgerrcht, E., Fridriksson, J., Rorden, C., & Bonilha, L. (2017). Connectome-based lesion-symptom mapping (CLSM): A novel approach to map neurological function. *NeuroImage: Clinical*, 16, 461–467. <https://doi.org/10.1016/J.NICL.2017.08.018>.
- Gvion, A., & Friedmann, N. (2012). Phonological short-term memory in conduction aphasia. *Aphasiology*, 26(3–4), 579–614. <https://doi.org/10.1080/02687038.2011.643759>.
- Halai, A. D., Woollams, A. M., & Lambon Ralph, M. A. (2018). Triangulation of language-cognitive impairments, naming errors and their neural bases post-stroke. *NeuroImage: Clinical*, 17, 465–473. <https://doi.org/10.1016/J.NICL.2017.10.037>.
- Hartwigsen, G., & Saur, D. (2017). Neuroimaging of stroke recovery from aphasia – Insights into plasticity of the human language network. *NeuroImage*. <https://doi.org/10.1016/J.NEUROIMAGE.2017.11.056>.
- Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, 8, 393–402.
- Hickok, G., Houde, J., & Rong, F. (2011). Sensorimotor integration in speech processing:

- Computational basis and neural organization. *Neuron*, 69(3), 407–422. <https://doi.org/10.1016/j.neuron.2011.01.019>.
- Hickok, G., & Poeppel, D. (2015). Neural basis of speech perception. *Handbook of Clinical Neurology*, 129, 149–160. <https://doi.org/10.1016/B978-0-444-62630-1.00008-1>.
- Hickok, G., & Poeppel, D. (2016). Chapter 25 – Neural Basis of Speech Perception. In G. Hickok, S. L. B. T.-N. of L. Small (Eds.) (pp. 299–310). San Diego: Academic Press. <https://doi.org/10.1016/B978-0-12-407794-2.00025-0>.
- Hope, T. M. H., Prejawa, S., Jones, Parker, Oberhuber, M., Seghier, M. L., Green, D. W., & Price, C. J. (2014). Dissecting the functional anatomy of auditory word repetition. *Frontiers in Human Neuroscience*, 8, 246. <https://doi.org/10.3389/fnhum.2014.00246>.
- Hope, T. M. H., Seghier, M. L., Prejawa, S., Leff, A. P., & Price, C. J. (2016). Distinguishing the effect of lesion load from tract disconnection in the arcuate and uncinate fasciculi. *NeuroImage*, 125, 1169–1173. <https://doi.org/10.1016/j.neuroimage.2015.09.025>.
- Hylin, M. J., Kerr, A. L., & Holden, R. (2017). Understanding the mechanisms of recovery and/or compensation following injury. *Neural Plasticity*, 2017, 1–12. <https://doi.org/10.1155/2017/7125057>.
- Jeanette, Y., Keller, E., & Lecours, A. (1980). Sequences of phonemic approximations in aphasia. *Brain and Language*, 11(1), 30–44.
- Kay, J., Lesser, R., & Coltheart, M. (1992). *PALPA. psycholinguistic assessments of language processing in aphasia*. Hove: Lawrence Erlbaum Associates.
- Kertesz, A. (1982). *The Western aphasia battery*. New York: Grune and Stratton.
- Kertesz, A., Pascual-Leone, A., Pascual-Leone García, A. (1990). Batería de afasias "Western": (the western aphasia battery en versión y adaptación castellana). Manual del test. Valencia: Nau, D.I.
- Kleist, R. (1931). Über Leitungssphasie. *European Neurology*, 80(3–4), 188–205.
- Kohn, S. E., & Friedman, R. B. (1986). Word-meaning deafness: A phonological-semantic dissociation. *Cognitive Neuropsychology*, 3(3), 291–308. <https://doi.org/10.1080/02643298608253361>.
- Kümmeler, D., Hartwiegse, G., Kellmeyer, P., Glauke, V., Mader, I., Klöppel, S., ... Saur, D. (2013). Damage to ventral and dorsal language pathways in acute aphasia. *Brain*, 136(2), 619–629. <https://doi.org/10.1093/brain/aws354>.
- Lee, Y. S., Zreik, J. T., & Hamilton, R. H. (2017). Patterns of neural activity predict picture-naming performance of a patient with chronic aphasia. *Neuropsychologia*, 94, 52–60. <https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2016.11.010>.
- López-Barroso, D., Catani, M., Ripolles, P., Dell'Acqua, F., Rodríguez-Fornells, A., & de Diego-Balaguer, R. (2013). Word learning is mediated by the left arcuate fasciculus. *Proceedings of the National Academy of Sciences*, 110(32), 13168–13173. <https://doi.org/10.1073/pnas.1301696110>.
- López-Barroso, D., & de Diego-Balaguer, R. (2017). Language learning variability within the dorsal and ventral streams as a cue for compensatory mechanisms in aphasia recovery. *Frontiers in Human Neuroscience*, 11, 476. <https://doi.org/10.3389/fnhum.2017.00476>.
- López-Barroso, D., de Diego-Balaguer, R., Cunillera, T., Camara, E., Münte, T. F., & Rodriguez-Fornells, A. (2011). Language learning under working memory constraints correlates with microstructural differences in the ventral language pathway. *Cerebral Cortex* (New York, N.Y.: 1991), 21(12), 2742–50. <https://doi.org/10.1093/cercor/bhr064>.
- López-Barroso, D., Ripollés, P., Marco-Pallarés, J., Mohammadi, B., Münte, T. F., Bachoud-Lévi, A.-C., ... de Diego-Balaguer, R. (2015). Multiple brain networks underpinning word learning from fluent speech revealed by independent component analysis. *NeuroImage*, 110, 182–193. <https://doi.org/10.1016/j.neuroimage.2014.12.085>.
- Makris, N., & Pandya, D. N. (2009). The extreme capsule in humans and rethinking of the language circuitry. *Brain Structure and Function*, 213(3), 343–358. <https://doi.org/10.1007/s00429-008-0199-8>.
- Marchina, S., Zhu, L. L., Norton, A., Zipse, L., Wan, C. Y., & Schlaug, G. (2011). Impairment of speech production predicted by lesion load of the left arcuate fasciculus. *Stroke*, 42(8), 2251–2256. <https://doi.org/10.1161/STROKEAHA.110.606103>.
- McKinnon, E. T., Fridriksson, J., Glenn, G. R., Jensen, J. H., Helpman, J. A., Basilakos, A., ... Bonilha, L. (2017). Structural plasticity of the ventral stream and aphasia recovery. *Annals of Neurology*, 82(1), 147–151. <https://doi.org/10.1002/ana.24983>.
- Mesulam, M.-M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology*, 28(5), 597–613. <https://doi.org/10.1002/ana.410280502>.
- Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B., & Schwartz, M. F. (2015). Neural organization of spoken language revealed by lesion–symptom mapping. *Nature Communications*, 6(1), 6762. <https://doi.org/10.1038/ncomms7762>.
- Nadeau, S. E. (2001). Phonology: A review and proposals from a connectionist perspective. *Brain and Language*, 79(3), 511–579. <https://doi.org/10.1006/blrn.2001.2566>.
- Poppenrey, U., Friston, K. J., & Price, C. J. (2004). Degenerate neuronal systems sustaining cognitive functions. *Journal of Anatomy*, 205(6), 433–442. <https://doi.org/10.1111/j.0022-872X.2004.00343.x>.
- Nozari, N., & Dell, G. S. (2013). How damaged brains repeat words: A computational approach. *Brain and Language*, 126(3), 327–337. <https://doi.org/10.1016/j.bandl.2013.07.005>.
- Ownsworth, T., Fleming, J., Tate, R., Beadle, E., Griffin, J., Kendall, M., ... Shum, D. H. K. (2017). Do people with severe traumatic brain injury benefit from making errors? A randomized controlled trial of error-based and errorless learning. *Neurorehabilitation and Neural Repair*, 31(12), 1072–1082. <https://doi.org/10.1177/1545968317740635>.
- Papagno, C., Comi, A., Riva, M., Bizzì, A., Vernice, M., Casarotti, A., ... Bello, L. (2017). Mapping the brain network of the phonological loop. *Human Brain Mapping*, 38(6), 3011–3024.
- Pate, D. S., Saffran, E. M., & Martin, N. (1987). Specifying the nature of the production impairment in a conductionaphasic: A case study. *Language and Cognitive Processes*, 2(1), 43–84. <https://doi.org/10.1080/01690968708406351>.
- Pick, A. (1924). On the pathology of echographia. *Brain*, 47(4), 417–429. <https://doi.org/10.1080/brain/47.4.417>.
- Postman-Caucheteux, W. A., Birn, R. M., Pursley, R. H., Butman, J. A., Solomon, J. M., Picchioni, D., ... Braun, A. R. (2010). Single-trial fMRI shows contralateral activity linked to overt naming errors in chronic aphasic patients. *Journal of Cognitive Neuroscience*, 22(6), 1299–1318. <https://doi.org/10.1162/jocn.2009.21261>.
- Rauschecker, A. M., Deutsch, G. K., Ben-Shachar, M., Schwartzman, A., Perry, L. M., & Dougherty, R. F. (2008). Reading impairment in a patient with missing arcuate fasciculus. *Neuropsychologia*, 47(1), 180–194. <https://doi.org/10.1016/j.neuropsychologia.2008.08.011>.
- Rauschecker, J. P., & Scott, S. K. (2009). Maps and streams in the auditory cortex: Nonhuman primates illuminate human speech processing. *Nature Neuroscience*, 12(6), 718–724. <https://doi.org/10.1038/nn.2331>.
- Restle, J., Murakami, T., & Ziemann, U. (2012). Facilitation of speech repetition accuracy by theta burst stimulation of the left posterior inferior frontal gyrus. *Neuropsychologia*, 50(8), 2026–2031. <https://doi.org/10.1016/j.neuropsychologia.2012.05.001>.
- Riddoch, M. J., & Humphreys, G. (1993). *Birmingham object recognition battery*. Hove, UK: Lawrence Erlbaum Associates.
- Rijntjes, M., Weiller, C., Bormann, T., & Musso, M. (2012). The dual loop model: Its relation to language and other modalities. *Frontiers in Evolutionary Neuroscience*, 4, 9. <https://doi.org/10.3389/fnevo.2012.00009>.
- Rojkova, K., Volle, E., Urbanski, M., Humbert, F., Dell'Acqua, F., & Thiebaut de Schotten, M. (2016). Atlasing the frontal lobe connections and their variability due to age and education: A spherical deconvolution tractography study. *Brain Structure and Function*, 221(3), 1751–1766. <https://doi.org/10.1007/s00429-015-1001-3>.
- Rolheiser, T., Stamatakis, E. A., & Tyler, L. K. (2011). Dynamic processing in the human language system: Synergy between the arcuate fascicle and extreme capsule. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(47), 16949–16957. <https://doi.org/10.1523/JNEUROSCI.2725-11.2011>.
- Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, 12(4), 191–200. <https://doi.org/10.1155/2000/421719>.
- Rosso, C., Vargas, P., Valabregue, R., Arbizu, C., Henry-Amar, F., Leger, A., ... Samson, Y. (2015). Aphasia severity in chronic stroke patients. *Neurorehabilitation and Neural Repair*, 29(3), 287–295. <https://doi.org/10.1177/1545968314543926>.
- Rubens, A. B., & Kertesz, A. (1983). The localization of lesions in transcortical aphasias. In A. Kertesz (Ed.). *Localization in Neuropsychology*(pp. 245–268). New York: Academic Press.
- Sarasso, S., Määttä, S., Ferrarelli, F., Poryazova, R., Tononi, G., & Small, S. L. (2014). Plastic changes following imitation-based speech and language therapy for aphasia: A high-density sleep EEG study. *Neurorehabilitation and Neural Repair*, 28(2), 129–138. <https://doi.org/10.1177/1545968313498651>.
- Saur, D., Kreher, B. W., Schnell, S., Kümmeler, D., Kellmeyer, P., Vry, M.-S., ... Weiller, C. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences of the United States of America*, 105(46), 18035–18040. <https://doi.org/10.1073/pnas.0805234105>.
- Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval: Voxel-based lesion-symptom mapping evidence from aphasia. *Brain: A Journal of Neurology*, 132(Pt 12), 3411–3427. <https://doi.org/10.1093/brain/awp284>.
- Shalllice, T., & Warrington, E. K. (1977). Auditory-verbal short-term memory impairment and conduction aphasia. *Brain and Language*, 4(4), 479–491.
- Sierpowska, J., Gabarrós, A., Fernandez-Coello, A., Camins, Á., Castañer, S., Juncadella, M., ... Rodríguez-Fornells, A. (2017). Words are not enough: Nonword repetition as an indicator of arcuate fasciculus integrity during brain tumor resection. *Journal of Neurosurgery*, 126(2), 435–445. <https://doi.org/10.3171/2016.2.JNS151592>.
- Sollereder, S., Stark, J., & Pons, C. (2013). Qualitative Analysis of Conduite d'approche Behavior in a Person with Wernicke's Aphasia. *Procedia – Social and Behavioral Sciences*, 94, 125–126. <https://doi.org/https://doi.org/10.1016/j.sbspro.2013.09.060>.
- Spielmann, K., Durand, E., Marcotte, K., & Ansaldi, A. I. (2016). Maladaptive plasticity in aphasia: Brain activation maps underlying verb retrieval errors. *Neural Plasticity*, 2016, 1–11. <https://doi.org/10.1155/2016/4806492>.
- Spielmann, K., van de Sandt-Koenderman, W. M. E., Heijenbrok-Kal, M. H., & Ribbers, G. M. (2018). Transcranial Direct Current Stimulation Does Not Improve Language Outcome in Subacute Poststroke Aphasia. *Stroke, STROKEAHA.117.020197*. <https://doi.org/10.1161/STROKEAHA.117.020197>.
- Stengel, E. (1947). Speech disorders and mental disorders. In A. V. Reuck & M. O'Connor (Eds.), *Disorders of Language*. London: Churchill.
- Suzuki, T., Itoh, S., Hayashi, M., Kouono, M., & Takeda, K. (2009). Hyperflexia and ambient echolalia in a case of cerebral infarction of the left anterior cingulate cortex and corpus callosum. *Neurocase*, 15(5), 384–389. <https://doi.org/10.1080/13554790902842037>.
- Thiebaut de Schotten, M., Dell'Acqua, F., Ratius, P., Leslie, A., Howells, H., Cabanis, E., ... Catani, M. (2015). From phineas gage and monsieur leborgne to H.M.: Revisiting disconnection syndromes. *Cerebral Cortex*, 25(12), 4812–4827. <https://doi.org/10.1093/cercor/bhv173>.
- Thiebaut de Schotten, M., Tomaiuolo, F., Aiello, M., Merola, S., Silvetti, M., Lecce, F., ... Doricchi, F. (2014). Damage to white matter pathways in subacute and chronic spatial neglect: A group study and 2 single-case studies with complete virtual "in vivo" tractography dissection. *Cerebral Cortex*, 24(3), 691–706. <https://doi.org/10.1093/cercor/bhs351>.
- Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: Converging evidence from lesion and connectivity analyses.

- Frontiers in Systems Neuroscience*, 5, 1. <https://doi.org/10.3389/fnsys.2011.00001>.
- Tyler, L. K., Marslen-Wilson, W., & Stamatakis, E. A. (2005). Dissociating neuro-cognitive component processes: Voxel-based correlational methodology. *Neuropsychologia*, 43(5), 771–778. <https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2004.07.020>.
- Ueno, T., & Lambon Ralph, M. A. (2013). The roles of the "ventral" semantic and "dorsal" pathways in conduite d'approche: A neuroanatomically-constrained computational modeling investigation. *Frontiers in Human Neuroscience*, 7, 422. <https://doi.org/10.3389/fnhum.2013.00422>.
- Valle, F., & Cuetos, F. (1995). *EPLA: Evaluación del procesamiento lingüístico en la afasia*. Hove, UK: Lawrence Erlbaum Associates.
- Wallesch, C.-W. (1990). Repetitive verbal behaviour: Functional and neurological considerations. *Aphasiology*, 4(2), 133–154. <https://doi.org/10.1080/02687039008249066>.
- Wechsler, D. (1988). *WAIS: Escala de inteligencia de Wechsler para adultos (7a edición)*. Madrid: TEA ediciones.
- Weiller, C., Bormann, T., Saur, D., Musso, M., & Rijntjes, M. (2011). How the ventral pathway got lost – And what its recovery might mean. *Brain and Language*, 118(1–2), 29–39. <https://doi.org/10.1016/J.BANDL.2011.01.005>.
- Welbourne, S. R., Woollams, A. M., Crisp, J., & Lambon Ralph, M. A. (2011). The role of plasticity-related functional reorganization in the explanation of central dyslexias. *Cognitive Neuropsychology*, 28(2), 65–108. <https://doi.org/10.1080/02643294.2011.621937>.
- Yeatman, J. D., & Feldman, H. M. (2013). Neural plasticity after pre-linguistic injury to the arcuate and superior longitudinal fasciculi. *Cortex*, 49(1), 301–311. <https://doi.org/10.1016/j.cortex.2011.08.006>.