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Arcuate fasciculus variability and repetition: The left sometimes can be right

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ABSTRACT

Repetition ability is a major criterion for classifying aphasic syndromes and its status is helpful in the determination of the involved neural structures. It is widely assumed that repetition deficits correlate with injury to the left perisylvian core including the arcuate fasciculus (AF). However, descriptions of normal repetition despite damage to the AF or impaired repetition without AF involvement cast doubts on its role in repetition. To explain these paradoxes, we analyse two different aphasic syndromes – in which repetition is selectively impaired (conduction aphasia) or spared (transcortical aphasias) – in light of recent neuroimaging findings. We suggest that the AF and other white matter bundles are the anatomical signatures of language repetition and that individual variability in their anatomy and lateralisation may explain negative cases.

1. Introduction

At the beginning of the twenty first century the debate on localisation of aphasia is still alive with competition between holistic and localising positions (York, 2009). However, thanks to recent advances in neuroimaging it is possible to perform a close scrutiny of previous theories and predictions about the cerebral mechanisms underpinning language in normal and brain-damaged individuals. This seems likely through studies using positron emission tomography (PET) (Ohyama et al., 1996; Collette et al., 2001; Price and Crinion, 2005; Raboyeau et al., 2008), functional magnetic resonance imaging (fMRI) (Abo et al., 2004; Fernandez et al., 2004; Saur et al., 2008), and diffusion tensor imaging (DTI) tractography (Catani et al., 2005, 2007; Parker et al., 2005; Friederici, 2009a, 2009b; Thiebaut de Schotten et al., 2012; Catani et al., 2012). These methods have been used independently (Ohyama et al., 1996; Collette et al., 2001; Abo et al., 2004; Fernandez et al., 2004; Catani et al., 2005; Price and Crinion, 2005; Raboyeau et al., 2008), in combination (Saur et al., 2008; Propper et al., 2010; Bizzi et al., 2012), or even complemented with other ancillary procedures (neuropsychological testing, transcranial magnetic stimulation, intracarotid amytal testing) (Catani et al., 2007; Vernooij et al., 2007; Matsumoto et al., 2008) to obtain valuable information about the *in vivo* anatomy and function of brain areas devoted to language as well as about the white matter fibre pathways binding remote cortical areas in each cerebral hemisphere. Undoubtedly, the emergence of

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new empirical findings or the replication of previous anatomical observations using non-invasive tools is worthwhile, yet these advances open new questions and can eventually reactivate old debates (Yamada et al., 2007; Geldmacher et al., 2007; Bernal and Ardila, 2009; Friederici, 2009a, 2009b; Weiller et al., 2009; Ardila, 2010). Accordingly, refinement in the description of the anatomy, function and hemispheric asymmetry of white matter fibre tracts coupled with the identification of inter-hemispheric dissociation of major speech centres (lateralisation of Broca's area and Wernicke's area in different hemispheres) have aroused new controversies concerning the participation of the arcuate fasciculus (AF) and other white matter tracts in repetition (Bernal and Ardila, 2009; Ardila, 2010).

Below, we analyse the role of the AF and other white matter fibre pathways in conduction aphasia (CA) (Wernicke, 1966; Kohn, 1992) and transcortical aphasias (TAs) (Lichtheim, 1885; Berthier, 1999). Gaining additional knowledge on the role of neural pathways underpinning repetition in aphasia is important because it could directly inform prognosis (Hosomi et al., 2009) and rehabilitation (Schlaug et al., 2009). Available evidence indicates that the transformation of phonological input into output through repetition of non-words plays a role in learning new words (Jacquemot and Scott, 2006) perhaps by promoting synaptic modification in excitatory projections each time a stimulus is presented. Recent findings are in line with this argument. Repetition in errorless-learning therapies improves noun and verb naming in anomic patients presumably by enhancing reinforcement mechanisms (Conroy et al., 2009). Sentence repetition exercises alone (Kohn, 1990) or paired with the cholinesterase inhibitor donepezil improve not only repetition performance (Berthier et al., 2004), but gains are generalised to fluency and spontaneous speech in CA and to sentence comprehension in mild receptive aphasia (Francis et al., 2003). In addition, a computer-assisted aphasia therapy (IMITATE) combining audiovisual presentation of words and phrases with oral repetition of these stimuli is a promissory strategy to improve language function (Lee et al., 2010). Lastly, intensive therapies modulating intonation and rhythm through repetition (Melodic Intonation Therapy) ameliorate performance in production tasks amongst patients with chronic Broca's aphasia and most notably the observed benefits are associated with remodelling of the right AF (increases in number of fibres, length and volume) (Schlaug et al., 2009).

2. The neural basis of normal language repetition

Before examining the role of the AF in repetition in aphasia, it is pertinent to briefly summarise how the normal brain mediates language repetition. The functional anatomy of repetition has been firmly established in normal subjects using $H_2{}^{15}O$ PET (Ohyama et al., 1996; Price et al., 1996; Castro-Caldas et al., 1998; Collette et al., 2001; Klein et al., 2006) and fMRI (Burton et al., 2001; Abo et al., 2004; Saur et al., 2008). Repetition of single words and word lists produces a strong activation of both cerebral hemispheres in superior temporal and premotor cortices, whereas the same pattern of activation holds for non-word repetition, but only in the left hemisphere (Weiller et al., 1995; Collette et al., 2001; Saur et al., 2008). Complementary studies combining fMRI with DTI further show that superior temporal and premotor areas activated during sublexical repetition interact via the AF, whereas foci of activation in temporal and frontal cortices elicited by semantic comprehension paradigms are connected by the ventral stream (Saur et al., 2008). The scenario is wholly different in aphasic patients with left hemisphere lesions because of network reorganisation. PET and fMRI studies revealed that aphasic patients use different strategies to compensate for impaired repetition performance which in part depend upon the localisation of the structural lesion (Turkeltaub et al., 2011); some patients recruit networks surrounding the infarction in the left hemisphere (e.g., Heiss et al., 1999), whereas in others word and non-word repetition is mediated by the right hemisphere (Weiller et al., 1995; Ohyama et al., 1996; Abo et al., 2004).

3. Conduction and TAs: two sides of the same coin

CA and TAs represent paradigmatic examples of impaired and preserved repetition, respectively (Geschwind, 1965; Brown, 1975; Kohn, 1992; Berthier, 1999). Traditionally, impaired repetition in CA has been linked to involvement of the left AF and other white matter tracts (Wernicke, 1966; Geschwind, 1965; Kohn, 1992), whereas TAs have been attributed, but not always (Niessl von Mayendorf, 1911; Stengel, 1947; Berthier, 1999), to lesions that spare the left perisylvian area and the AF (isolation of the speech area) (Geschwind, 1965, 1968) (Fig. 1). In CA, a disproportionate deficit in repetition occurs in the context of fluent paraphasic verbal production and relative sparing of auditory comprehension (Geschwind, 1965; Goodglass, 1992). At least two types of CA have been described, *reproduction* and *repetition* (Shallice and Warrington, 1977; Nadeau, 2001). The reproduction subtype is characterised by phonemic paraphasias in all verbal domains and recurrent production of sequential phonemic approximations to self-repair errors (*conduit d'approche*) (Shallice and Warrington, 1977; Nadeau, 2001). Reproduction CA has been variously attributed to deficits in verbal praxis (Ardila and Rosselli, 1990), disrupted speech programming (Bernal and Ardila, 2009), poor output phonological encoding (Kohn, 1992; Bernal and Ardila, 2009), or a combination of abnormal sensory-motor integration and reduced phonological short-term memory (Buchsbaum et al., 2011; Hickok et al., 2011) which may result from cortical damage without obligatory involvement of the AF. The repetition subtype shows virtually isolated repetition deficits which have been linked to a selective impairment in auditory–verbal short-term memory and cortical damage that extend deeply to affect the AF (Shallice and Warrington, 1977; Kohn, 1992; Nadeau, 2001).

Note, however, that a clear-cut distinction between both forms of CA may be difficult to establish as they usually share some language deficits (e.g., phonological paraphasia, reduced auditory–verbal short-term memory) (Sakurai et al., 1998). Indeed, at present there is a true spectrum of syndromes meeting the diagnostic criteria for CA which could be, at least in part, explained by differences in aphasia severity, time of aphasia evaluation (acute *vs* chronic), type of repetition tasks

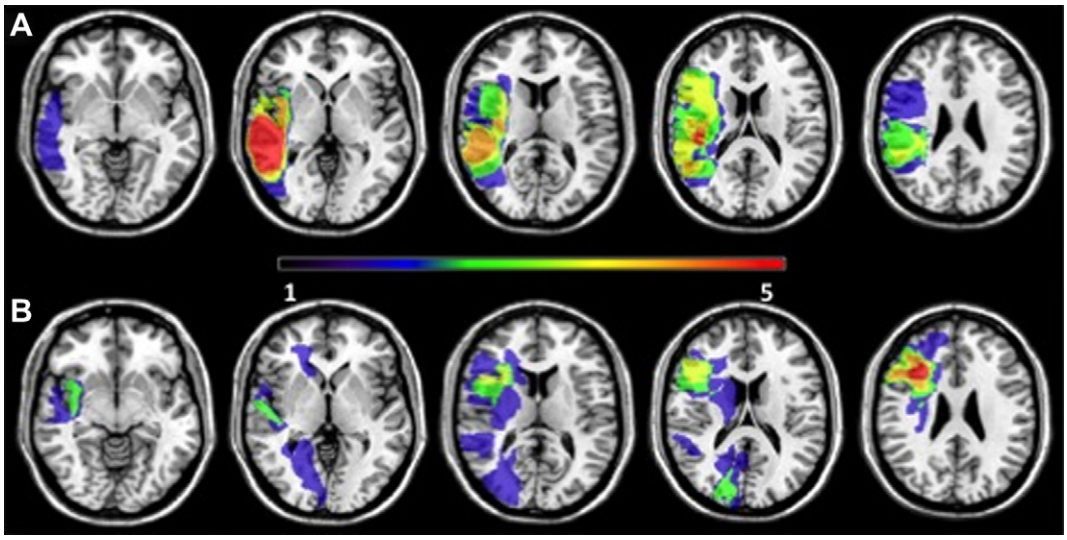

Fig. 1 – Lesion overlay of patients with two different aphasias. (A) Average lesion density in 5 patients with chronic *repetition* CA showing the greatest areas of lesion overlap in posterior–superior temporal gyrus, insular cortex and AF with additional involvement of Broca's area in some patients. The dorsal stream, ventral stream or both were affected in all patients. (B) Average lesion density in 5 patients with subacute and chronic transcortical sensory aphasia showing a heterogeneous distribution of lesions with some of them sparing the perisylvian language cortex, particularly the posterior–superior temporal gyrus, and others involving it (Broca's area, insula, anterior part of the AF). The colour bar indicates the number of patients contributing to the average lesion image in both groups.

used (immediate repetition *vs* delayed repetition), lesion localisation (suprasylvian *vs* infrasylvian), or compensatory mechanisms (residual language abilities mediated by spared areas of the left hemisphere, the right hemisphere, or both) (Nadeau, 2001). For example, the pattern of *repetition* CA may evolve during the recovery process from a more severe language disorder termed "deep dysphasia" (Martin et al., 1994), a condition that shows not only the phonological processing deficits (e.g., phonemic paraphasias, poor repetition of words and non-words) characteristic of CA, but also accompanying deficits affecting lexical-semantic representations (e.g., production of semantic errors in single word repetition) (Gold and Kertesz, 2001; Jefferies et al., 2007). Importantly, patients with *repetition* CA may behave as deep dysphasics under demanding testing conditions. Semantic errors of the kind described in deep dysphasia (e.g., "necklace" → *gold*) can be elicited in patients with CA when repetition is delayed or when word lists are presented for repetition (*see review in* Jefferies et al., 2007). Finally, "deep" disorders of reading aloud, repetition and spelling (Duhamel and Poncet, 1986; Schweiger et al., 1989; Rapcsak et al., 1991; Cardebat et al., 1994; Coltheart, 2000) and CA can reflect a partial reliance on right hemisphere activity (Kinsbourne, 1971; Demeurisse and Capon, 1991).

The other syndromes that have aroused interest regarding the status of repetition performance are the TAs. These aphasias are characterised by preserved repetition despite deficits in spontaneous speech (transcortical motor aphasia), auditory comprehension (transcortical sensory aphasia), or both (mixed TA) (Berthier, 1999). Traditionally, the TAs syndromes have been linked to lesions in the left extrasylvian cortical surface which disrupt the connectivity between frontal areas responsible for speech initiation (Alexander, 2006) or posterior conceptual-semantic representation areas and the intact perisylvian language core and its underlying white matter fibre pathways including the AF (Kertesz et al., 1982). However, patients with TAs and left perisylvian lesions that involve the AF have been described (Bando et al., 1986; Trojano et al., 1988; Berthier et al., 1991; Grossi et al., 1991; Pulvermüller and Schönle, 1993) and in some of them intracarotid amytal testing provided evidence of right hemisphere mediation of repetition (Bando et al., 1986; Berthier et al., 1991). It has been assumed that in such cases repetition is pre-morbidly organised in the right hemisphere or bilaterally and it is rapidly "released" as a result of decreased inhibition from the damaged left hemisphere (Bando et al., 1986; Berthier, 1999).

4. Repetition and the AF – controversies

The "disconnection" hypothesis of CA championed by Norman Geschwind (1965) posits that repetition is impaired because damage to the left AF and other fibre pathways travelling through the insular cortex interrupts the transmission between posterior (Wernicke's area) and anterior (Broca's area) cortical regions (Geschwind, 1965; Catani and Mesulam, 2008). This mechanism has been controversial since its original formulation by German researchers (*see* de Bleser et al., 1993; Weiller et al., 2011) and it has recently been claimed that the AF is not essential for repetition, an argument that downplays the "disconnection" account of CA in favour of the cortical mechanism (Anderson et al., 1999; Quigg and Fountain, 1999; Bartha and Benke, 2003; Quigg

et al., 2006; Geldmacher et al., 2007; Bernal and Ardila, 2009). The main arguments raised against the key role of the AF in language repetition amongst patients with CA are: (i) pure cortical damage sparing the AF is sufficient to impair repetition, (ii) selective damage to the left AF does not necessarily produce the expected deficit in repetition, and (iii) the identification of inter-hemispheric dissociation of major language centres (*left* Broca's area and *right* Wernicke's area) in normal subjects invalidates the disconnection account of CA (Bernal and Ardila, 2009). These arguments highlight that the role of the AF in repetition is still an open issue claiming for an integrative explanation. We concede that cortical damage may interfere with repetition activity, perhaps due to corrupted acoustic-phonological input to the AF following posterior–superior temporal gyrus damage or poor motor encoding from the output of the AF after inferior frontal lesion. However, taking advantage of the most recent advances in the imaging of white matter fibre pathways, our current position maintains that damage to the dorsal stream (AF), ventral stream (white matter tracts travelling through the extreme capsulae) or both are the specific signatures of impaired repetition in CA.

5. Is pure cortical involvement sufficient to impair repetition?

One controversial issue concerns whether damage to the left AF is required to impair repetition in CA or whether pure cortical involvement will suffice (*see* Fridriksson et al., 2010; Ross, 2010; Buchsbaum et al., 2011; Hickok et al., 2011). One piece of evidence used in favour of the exclusive cortical involvement comes from electrical stimulation studies performed in epileptic patients (Anderson et al., 1999; Quigg and Fountain, 1999; Quigg et al., 2006). Anderson et al. (1999) observed that stimulation delivered to the left posterior–superior temporal gyrus reproduced the clinical profile of CA. Such finding prompted these researchers to suggest that cortical dysfunction may lead to abnormal repetition in CA, perhaps by reducing the excitability of local small networks implicated in phonological processes during speech production. Interestingly, Anderson et al. (1999) also admitted that cortical stimulation may have caused dysfunction of pyramidal cells that give rise to the fibres that form the AF. Quigg and coworkers (Quigg and Fountain, 1999; Quigg et al., 2006) also found that electrical cortical stimulation in two epileptic patients induced an isolated deficit in language repetition during stimulation of the posterior portion of the dominant superior temporal gyrus in one patient and during stimulation of the supramarginal gyrus in the other patient. In another study carried out in 6 epileptic patients (Boatman et al., 2000) electrical interference in the same sites (left posterior–superior temporal gyrus) stimulated by both Anderson et al. (1999) and Quigg and Fountain (1999) elicited TCSA with preserved repetition instead of CA, possibly by disrupting the indirect AF segment binding phonology (temporal) and lexical-semantic (parietal) processing regions (Axer et al., 2001; Catani et al., 2005, 2007). In our view, the argument of involvement of the AF at its cortical origins is probably valid for patients with superficial cortical injury, but compelling evidence indicates that many patients with CA actually have large left temporal–parietal lesions that inexorably affect all segments of the AF, thus supporting the disconnection mechanism (Fig. 2). Even in cases of CA with restricted temporal cortical involvement (infrasylvian CA) (Axer et al., 2001) the responsible lesion disrupts the origins of the AF's direct segment in the temporal cortex and since it is close enough to the insular cortex the lesion may interrupt the ventral stream travelling in the extreme capsulae (Catani et al., 2005, 2007; Friederici, 2009a, 2009b; Weiller et al., 2011). The involvement of the AF is viewed as elusive when CA occurs in association with focal damage to the parietal cortex (suprasylvian CA) (Axer et al., 2001; Hickok and Poeppel, 2004), yet pathological studies of similar patients revealed that these lesions extended deeply to the lateral ventricle, interrupting the AF (Benson et al., 1973). Additionally, parietal damage in these latter cases may also disrupt the cortical origin of the AF's indirect segment severing its connections with the superior temporal cortex and lateral frontal cortices (Catani et al., 2005; Parker et al., 2005). In support to the data above, a recent DTI study in a group of aphasic patients ($n = 20$) with acute stroke found that abnormal repetition was independent of the degree of cortical damage in the left hemisphere, but it correlated significantly with damage to the left AF and superior longitudinal fasciculus (Breier et al., 2008). Other DTI studies also documented consistent involvement of the left AF in CA (Yamada et al., 2007; Zhang et al., 2010). Taken together, these results give more weight to the disconnection mechanism than to the cortical damage account as the likely mechanism for the different anatomical variants of CA (Geschwind, 1965).

6. Variability determines the status of repetition

Opponents to the participation of the AF in repetition processes have also build up their arguments on the basis of negative evidence (Shuren et al., 1995; Bernal and Ardila, 2009). Admittedly, lack of the expected effects of lesions exists and include cases in whom repetition performance remained intact after surgical ablation of the anterior left AF (Shuren et al., 1995) and cases of TAs coursing with well-preserved ability to repeat heard speech in spite of having extensive involvement of the AF, the insular cortex, or both (Bando et al., 1986; Berthier et al., 1991; Berthier, 2001; Selnes et al., 2002; Maeshima et al., 2004; Jefferies and Lambon Ralph, 2006; Kim et al., 2009). Conversely, defenders of the role of the AF in repetition maintain that focal vascular (Poncet et al., 1987; Tanabe et al., 1987) and demyelinating lesions (Arnett et al., 1996) restricted to the left AF are sufficient to alter repetition causing CA. Moreover, intraoperative subcortical stimulation of the AF (localised with DTI tractography), induces phonemic/semantic paraphasias and repetition disorders akin to those described in CA (Duffau, 2006; Leclercq et al., 2010; Duffau, 2012). How can these apparently divergent findings be reconciled? In our opinion, the instances of negative evidence, wherein damage to the left AF coursing without repetition disturbance, as occurs in TAs (Bando et al., 1986; Berthier, 1999, 2001; Shuren et al., 1995; Selnes et al.,

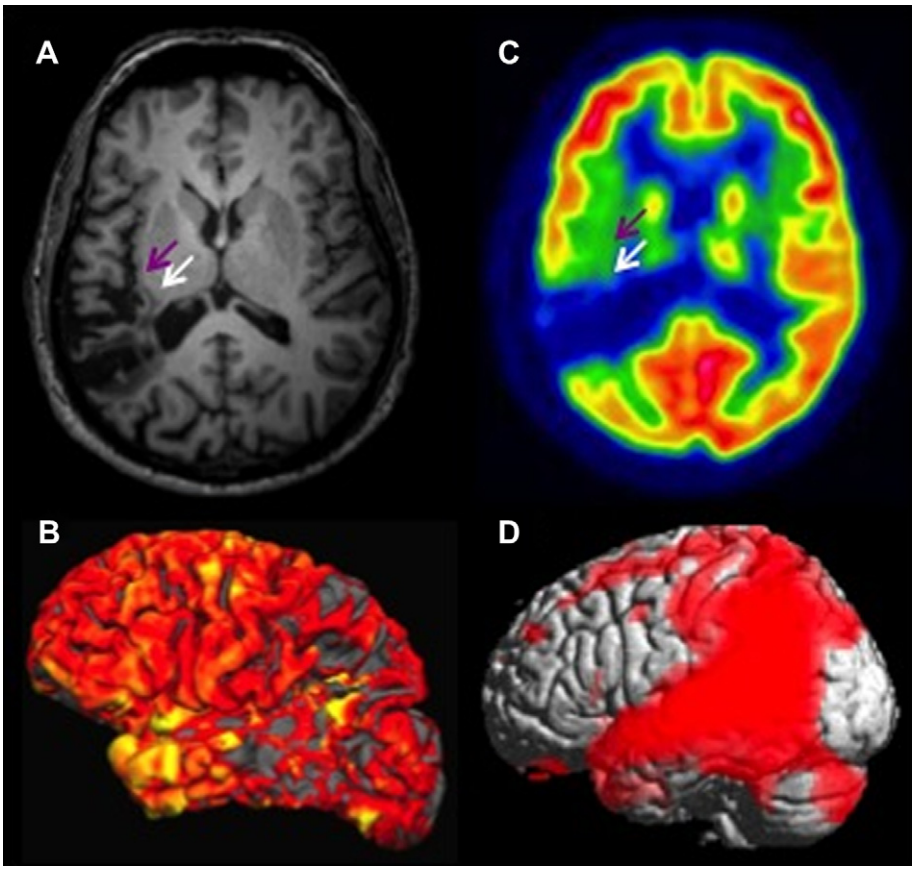

Fig. 2 – Structural and functional neuroimaging correlates of chronic *repetition* CA in a single case (patient AFR). (A) Structural 3-T MRI (axial plane) shows a left temporo-parietal infarction with subcortical extension into the AF (white arrow) and ventral stream in the posterior insular cortex (purple arrow). (B) Uninflated surface of the left hemisphere (FreeSurfer analysis) shows reduced cortical thickness (grey and yellow) in temporo-parietal regions. (C) ^{18}FDG-PET (axial plane) at rest depicting a focal area of decreased metabolism ($p < .001$ relative to 18 age- and gender-matched normal controls) affecting the left temporo-parietal cortex, AF (white arrow) and posterior insular cortex (purple arrow). (D) Brain surface rendering of ^{18}FDG-PET showing significantly decreased metabolism in the left hemisphere mainly affecting the left temporo-parietal cortex.

2002; Maeshima et al., 2004; Jefferies and Lambon Ralph, 2006; Kim et al., 2009), merit a reinterpretation. Recent DTI studies determine that the AF is structurally more complex than previously recognised as it is composed of different segments which by virtue of their cortical–cortical connectivity participate in distinct language functions (Catani et al., 2005, 2007; Parker et al., 2005; Matsumoto et al., 2008; Vernooij et al., 2007; Saur et al., 2008; Friederici, 2009a, 2009b). Thus, compromise of different AF's segments by focal injury could account for instances of negative evidence. Catani et al. (2005) argued that selective lesions involving one AF segment are associated with normal performance in some repetition tasks, but with impaired performance in others. Consider, for example, the double dissociation between repetition of novel sentences and clichés ("Who laughs last, laughs longest") found in patients with CA and TAs (McCarthy and Warrington, 1984; Berthier, 2001). In CA, repetition of novel sentences is better than clichéd repetition, a pattern of performance that has been linked with damage to the direct long segment and sparing of both the indirect segment and the ventral stream pathway implicated in the active semantic processing required for novel sentence repetition (McCarthy and Warrington, 1984; Catani et al., 2005, 2007; Parker et al., 2005; Saur et al., 2008). Conversely, better repetition of clichés than of novel sentences occurs in TAs and this pattern has been associated with focal injury to the indirect pathway that spared the direct segment implicated in the fast, automatic repetition of familiar over-learned idiomatic phrases (McCarthy and Warrington, 1984; Catani et al., 2005, 2007; Parker et al., 2005; Saur et al., 2008).

A second prediction to account for an instance of negative evidence is based in the intra- and inter-hemispheric variability of white matter pathways (Catani et al., 2005, 2007; Gharabaghi et al., 2009). DTI studies have shown that besides the lateral asymmetries of the perisylvian language cortex and its underlying white matter (Pujol et al., 2002; Takao et al., 2010), impressive structural variability and asymmetries are also observable in the white matter language-related pathways (Catani et al., 2005, 2007; Parker et al., 2005; Vernooij et al., 2007; Friederici, 2009a, 2009b).

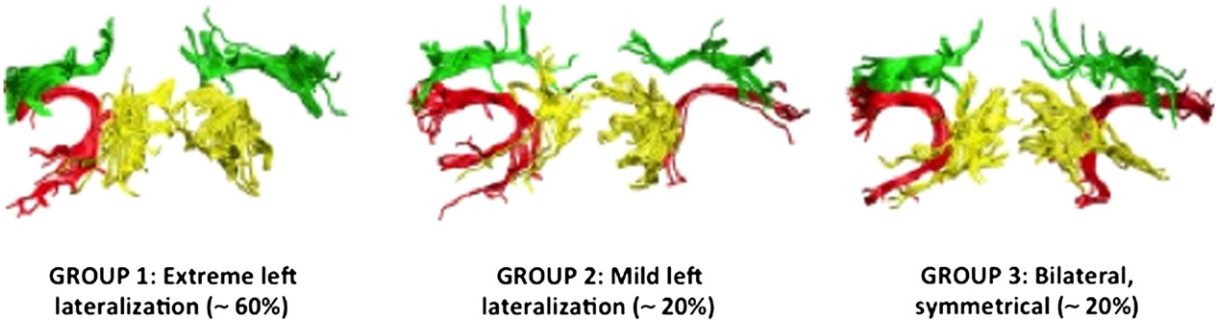

Fig. 3 – Distribution of hemispheric lateralisation of the AF (long segment is depicted in red) in normal subjects (reprinted from Catani and Mesulam, *Cortex*, 44 (8): 953–961, 2008). In the text it is suggested that lesion in posterior left perisylvian area in subjects of Groups 1 and 2 might cause CA, whereas similar lesions in subjects of Group 3 might cause TAs.

Addressing first the anatomic variability of the AF in the left hemisphere, one interesting piece of evidence is the observed anatomical difference in the direct segment of the AF between individuals, with some subjects showing a strong portion of this segment, whereas vestigial development is found in others (Catani et al., 2007; Vernooij et al., 2007). A hypothesis parsimonious with the results of these previous studies (Catani et al., 2007; Vernooij et al., 2007) is that small left subcortical lesions in patients having a less voluminous AF may not induce repetition disturbance because its long direct segment has escaped from being damaged. This interpretation, however, is only speculative and requires confirmation with DTI studies.

A third proposition is that inter-individual variability in the hemispheric lateralisation of the AF is responsible from the lack of the expected repetition impairment in patients with lesions of the left AF. Most studies did find extreme leftward lateralisation (60–80%) of the direct segment and extremely undeveloped or even absent right direct segment of the AF, a pattern that seems to be the critical anatomical substrate for language lateralisation (Catani et al., 2005, 2007; Vernooij et al., 2007; Matsumoto et al., 2008). Other 10–20% of individuals have mild leftward lateralisation of the AF and the remaining 20% have bilateral symmetrical pattern (Catani et al., 2005, 2007; Vernooij et al., 2007) (Fig. 3). Interestingly enough, individuals having the symmetrical pattern show better verbal recall (repetition) in memory tasks of semantically-related words than those having an extreme leftward lateralisation, presumably because individuals of the former group additionally recruit the right AF during word recall (Catani et al., 2007). This data could contribute to understand why some right-handed patients with left temporal–parietal lesions develop CA (Benson et al., 1973; Kohn, 1992), whereas others with similar allocated lesions instead display aphasias with normal repetition performance (TAs) (Bando et al., 1986; Berthier, 1999). In other words, it could be speculated that patients with CA might have enduring and long-lasting repetition deficits because they have extreme leftward lateralisation of the AF and a too small right AF to be efficient in compensating the repetition deficit. Conversely, patients with similar lesions but developing TAs might have more symmetrical patterns with both AF engaging repetition pre-morbidly or with the right AF rapidly assuming repetition duties after being released from the control of the homotopic regions in the left hemisphere (Berthier, 1999). There might be a fourth explanation – given the evidence for a ventral route – it could be that the ventral stream (a) is more involved in language repetition pre-morbidly in some people (Carota et al., 2007), or (b) is capable of picking up repetition duties through post-injury plasticity (Welbourne and Lambon Ralph, 2007).

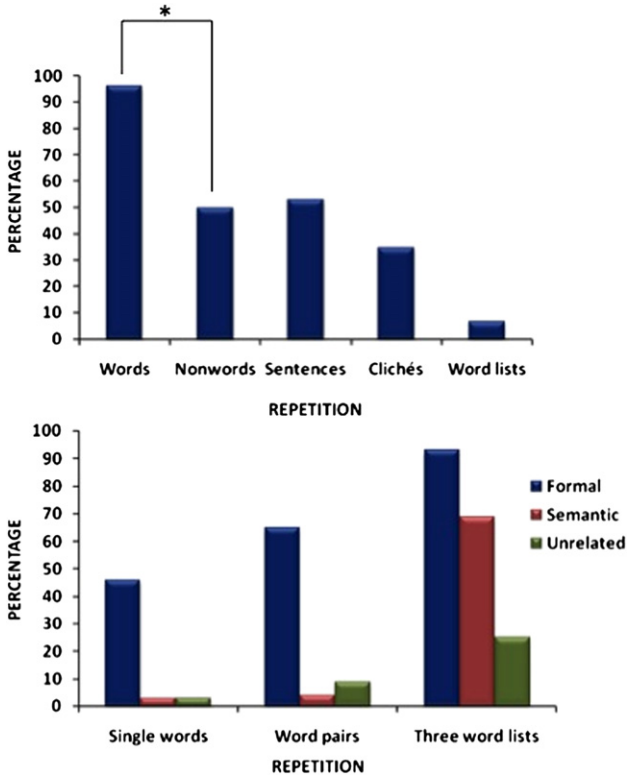

Fig. 4 – Performance of patient JVA on repetition tasks (left graph) and pattern of errors during repetition (right graph). *$p < .005$.

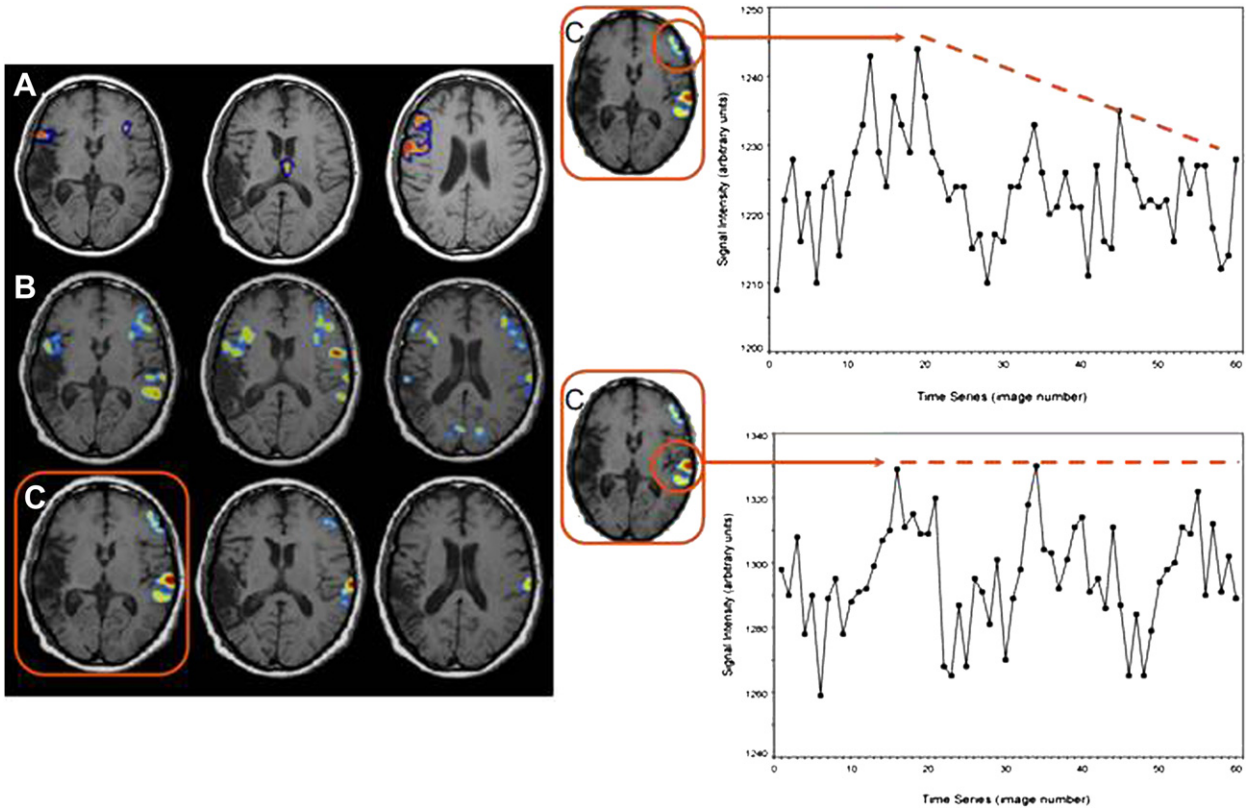

Fig. 5 – Brain activation during repetition in patient JVA with *repetition* CA. (A) Left premotor prefrontal activation and a small right frontal activation focus during covert non-word repetition. (B) Right posterior–superior temporal gyrus and bilateral frontal and anterior insula activations during covert word repetition. (C) Exclusive right hemisphere activation during covert repetition of three-word lists in right posterior–superior temporal gyrus and right prefrontal gyrus. Time series analysis during three-word repetition in this slice (C) shows consistent right posterior–superior temporal gyrus signal intensity (right panel, bottom) and decay of right frontal signal intensity (right panel, top). Statistical threshold was set at $p < .001$, uncorrected.

7. Atypical patterns of language lateralisation

The final argument raised against the role of the AF damage in CA is based on the lack of overt speech and language deficits among normal subjects with fMRI evidence of an atypical pattern of inter-hemispheric language lateralisation (Broca's area residing in one hemisphere and Wernicke's area in the other) (Bernal and Ardila, 2009). This is not a trivial issue, because dissociated hemispheric lateralisation of language production and language comprehension is not exceptional in normal right-handed subjects (Lidzba et al., 2011). In our view, this repartition of major language functions in separate hemispheres does not invalidate the disconnection account of CA. Rather, it reminds us of a commonly forgotten mechanism underlying CA, originally proposed by the German neurologist Karl Kleist (1934). He described patients with CA who in spite of having massive destruction of the left posterior–superior gyrus (Wernicke's area) had normal auditory comprehension (Kleist, 1934). The complete destruction of the left Wernicke's area in CA has been confirmed in clinico-pathological (case 2 in Benson et al., 1973) and structural imaging studies (Mendez and Benson, 1985). In addition, the participation of the right hemisphere in comprehension has been demonstrated in an autopsied case with complete destruction of left Wernicke's area and normal language comprehension (Boller, 1973) as well as using intracarotid amytal injections (Kinsbourne, 1971) and functional neuroimaging (Demeurisse and Capon, 1991). Taken as a whole, these findings reveal that the right Wernicke's area may be engaged in auditory comprehension pre-morbidly or gradually after the left hemisphere injury, and also demonstrate that CA may occur in cases where the Wernicke's area resides in the hemisphere contralateral to the Broca's area (Kinsbourne, 1971; Benson et al., 1973; Mendez and Benson, 1985; Berthier et al., 2010). However, there are still some unanswered questions. Two in particular stand out: (i) how repetition is accomplished in these patients? and (ii) would the disconnection account apply?

Functions of the dominant left AF have been discussed for more than a century (Geschwind, 1965), but little is known about the participation of its homologous counterpart in the repetition processes of aphasic patients. Functional recovery in CA depends on compensatory plasticity with reallocation of language in the right hemisphere and of undamaged

neural networks of the left hemisphere (Fernandez et al., 2004). Recovery of single word comprehension and word repetition after complete destruction of the left Wernicke's area may be complete (Weiller et al., 1995; Price, 2000), yet performance in more demanding tasks (repetition of non-words, word lists, and sentences) is usually abnormal. Findings from repetition performance of the patient JVA described below may be instructive in this regard (Berthier et al., 2005).

8. Functional analysis of residual repetition in CA

Recently, we studied the functional correlates of repetition with fMRI in a right-handed male patient, JVA, with long-standing *repetition* CA associated to a left temporo-parietal and posterior insular infarction (Berthier et al., 2005). Testing with the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Kay et al., 1992; Valle and Cuetos, 1995) revealed that JVA had unimpaired auditory processing [minimal non-word pairs (.91), minimal word pairs (.98), and lexical decision (.98)], with preserved lexical-semantic processing (spoken word–picture matching: 1.0) and mildly impaired sentence processing (spoken sentence–picture matching: .82). He had a slight impairment in picture naming (naming by frequency: .87) but the rest of his speech production was intact (fluency in spontaneous speech: 9.8/10). Word repetition was intact (1.0), but repetition of non-words (.48) and sentences (.50) was moderately impaired and sentence repetition was better for novel sentences than idiomatic clichés (Fig. 4). Digit span was 3 in the forward condition. In repetition of three-word lists composed of high-frequency words conveying constrained semantic information ("*eat-green-apple*") (McCarthy and Warrington, 1984; Berthier, 2001) his performance was poor (.08) and there was a marked "lexical bias" with formal and semantic paraphasias (Fig. 4). The fMRI study in JVA showed that single word and non-word repetition significantly activated the right primary auditory cortex, the right superior temporal gyrus and the dorsolateral prefrontal region bilaterally. Imaging data during repetition of three-word lists with meaningful semantic information showed activation exclusively of a right hemisphere network that included the primary auditory cortex, the posterior part of the superior temporal gyrus and the prefrontal cortex (Fig. 5). A time course analysis of signal intensity during repetition of sequences of three-word lists shows consistent right posterior–superior temporal gyrus signal intensity and a decay of activation from the first activation block to the third activation block in the right frontal region.

It seems that in JVA the left temporo-parietal and insular infarction impeded auditory input to this hemisphere, yet his performance in receptive word phonology and lexical-semantics was preserved. Therefore, the consistent right temporal lobe activation observed in fMRI during repetition of words, non-words and word lists indicates that incoming auditory information was processed in the right superior temporal gyrus, encoded and then transferred to frontal regions. Bifrontal activation under word and non-word repetition conditions suggests a multistep transfer of verbal activation to the left frontal cortex, a key region in processing verbal output in normal conditions. In the case of repeating lists of real-words, a similar compensatory strategy may be adopted, but success to reach the left frontal cortex was impossible, presumably due to pathologically rapid decay of activation in the semantic–lexical–phonological network in combination with a restricted auditory–verbal short-term memory (Martin, 1996; Gold and Kertesz, 2001; Jefferies et al., 2007). Thus, it seems that the co-activation of eloquent regions in both hemispheres is sufficient for maintaining normal word repetition. However, when the translation of auditory input to phonological output is overloaded (e.g., word list repetition) performance accuracy decreases such that formal and semantic errors emerge.

9. Conclusions and directions for future research

The reviewed data suggest that the AF and other white matter bundles are the anatomical signatures of repetition and that individual variability in their anatomy and lateralisation may explain negative cases. Some outstanding questions need to be addressed in future research, however. What is the balance of dorsal (AF) versus ventral (extreme capsule) streams in normal and impaired repetition? What are the roles of the various divisions of the AF in language versus non-language processing? How does the involvement of right hemisphere pathways and non-AF routes (small networks) in the dominant hemisphere change during recovery and partial-recovery after stroke? Hopefully, future structural and functional neuroimaging studies in aphasic patients will illuminate these issues.

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