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A re-examination of neural basis of language processing: Proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming

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ABSTRACT

From recent findings provided by brain stimulation mapping during picture naming, we re-examine the neural basis of language. We studied structural–functional relationships by correlating the types of language disturbances generated by stimulation in awake patients, mimicking a transient virtual lesion both at cortical and subcortical levels (white matter and deep grey nuclei), with the anatomical location of the stimulation probe. We propose a hodotopical (delocalized) and dynamic model of language processing, which challenges the traditional modular and serial view. According to this model, following the visual input, the language network is organized in parallel, segregated (even if interconnected) large-scale cortico-subcortical sub-networks underlying semantic, phonological and syntactic processing. Our model offers several advantages (i) it explains double dissociations during stimulation (comprehension versus naming disorders, semantic versus phonemic paraphasias, syntactic versus naming disturbances, plurimodal judgment versus naming disorders); (ii) it takes into account the cortical and subcortical anatomic constraints; (iii) it explains the possible recovery of aphasia following a lesion within the "classical" language areas; (iv) it establishes links with a model executive functions.

1. Introduction

For more than a century, lesion studies on aphasiology have led to a localisationist view of language organization, in which Broca's and Wernicke's areas are assigned the leading roles in language production and comprehension, respectively. Nonetheless, anatomo-functional correlations based on lesion method suffer from many limitations. The first is the size of the injuries, which are often extensive, especially in stroke. Secondly, the accurate three dimensional delineation of damages was very difficult until development of MRI. Indeed, recent MRIs of Leborgne's and Lelong's brain showed wide injuries involving not only the classical "Broca's area" but also the insula and perisylvian white matter (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007) – meaning that the "motor aphasia" did not necessarily result from lesion to the inferior frontal operculum. Thirdly, in lesion maps, it is dangerous to interpret that a "statistical epicenter" common to every patients is the region which sub-served the disturbed function. In fact, the same neurological deficit may be due to damages in different locations across patients, all of them being involved in a large functional network around (but not including) the "epicenter" thought to be crucial. Finally, compensatory mechanisms of post-lesional plasticity can also occur, especially in slow-growing lesions (Desmurget, Bonnetblanc, & Duffau, 2007; Duffau, 2005).

Advances in functional neuroimaging have recently enabled to provide new insights into the neural basis of language, both in aphasic patients and healthy volunteers (Vigneau et al., 2006). Nonetheless, it is worth noting that these techniques, even if they do not have the pitfalls of lesion method, are based on the principle of "activations" during task performance and paradoxically lost the major advantage of lesion studies, that is, the correlation of structure with functional disturbances. In other words, it is not because an area has been activated on fMRI that its destruction will cause a deficit.

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Here, our goal is to re-examine the neural foundations of language on the basis of data issued from direct electrical stimulation (DES) of the brain in awake patients. Indeed, during surgery for a lesion (such as a tumor) invading both cortical and subcortical structures, it has become common clinical practice to awaken patients in order to assess the functional role of restricted cerebral regions (the brain has no receptors for pain). The surgeon can maximize the extent of resection, and thereby improve the overall survival, without generating functional (especially language) impairments, thanks to an individual mapping and preservation of eloquent structures: it means that the resection is performed according to functional boundaries (Duffau, 2007; Duffau, Gatignol, Mandonnet, Capelle, & Taillandier, 2008). Concretely, patients perform several language tasks, such as counting or picture naming, while the surgeon temporarily interacts with discrete areas within the grey and white matter around the tumor, using DES. If the patients stops speaking or produces wrong response, the surgeon avoid removing the stimulated site (Duffau, 2011; Duffau et al., 2002). Although the exact mechanism of DES remains unknown, the usual view is that DES transiently interacts locally with a small cortical or axonal site, but also non-locally, as the focal perturbation will indeed disrupt the whole (sub-)network sustaining a given function (Mandonnet, Winkler, & Duffau, 2010). Therefore, conversely to functional neuroimaging, DES induces a transient virtual lesion, by inhibiting a sub-circuit during approximately 4 s, with the possibility to check whether the same language disorders are reproduced when repeated stimulations are applied over the same area. Interestingly, by gathering all cortical and axonal sites where the same type of errors have been observed when stimulated, one would build up the sub-network of the disrupted subfunction. As a consequence, DES was extensively demonstrated to represent a unique opportunity to identify with a great accuracy (about 5 mm) and reproducibility, in vivo in humans, the structures that are crucial for cognitive functions, especially language, both at cortical and subcortical (white matter and deep grey nuclei) levels. In addition, combining language disturbances elicited by intrasurgical DES with the anatomical data provided by pre- and post-operative MRI has enabled to perform reliable anatomo-functional correlations (Duffau, 2011; Duffau et al., 2002).

We will review the original data provided by intraoperative DES during awake surgery within the left dominant hemisphere to propose a revisited model of language, switching from a modular to a hodotopical (delocalized) and dynamic view, in which language is conceived as resulting from parallel processing performed by distributed groups of connected and synchronized neurons, rather than by individual centers (Duffau, 2008). In this framework, language is underlain by large-scale sub-networks interacting together and able to compensate themselves after brain lesion (at least to some degrees), opening the door to brain plasticity. In pathology, according to this new concept, a topological mechanism (from the Greek *topos* = place) refers to a dysfunction of the cortex (deficit, hyperfunction or a combination of both), whereas a hodological mechanism (from the Greek *hodos* = road or path) refers to dysfunction related to connecting pathways (disconnection, hyperconnection or a combination of both) (Catani, 2007; de Benedictis & Duffau, 2011). In other words, it is mandatory to take into account the complex functioning of a wide distributed circuit to understand both its physiology as well as the functional consequences of a lesion of this network – with possible distinct deficits depending on the location and the extent of damage (e.g. purely cortical, or purely subcortical, or both).

Of note, the picture naming task has extensively been used in the literature for intraoperative language mapping in awake patients (Ojemann, Ojemann, Lettich, & Berger, 1989; Sanai, Mirzadeh, & Berger, 2008). Indeed, this is a very sensitive test which involves a large network, thus adapted for the surgical conditions, due to the limitation of time for mapping (about 2 h). Consequently, we will take picture naming as main paradigm in our review, even if other tasks will be considered throughout the manuscript. In a first part, we will correlate the different types of errors elicited by DES stimulation during a picture naming task with the "classical" LRM model of spoken word production (Levelt, Roelofs, & Meyer, 1999) which will serve as a reference. In a second paragraph, we will study structural–functional relationships by correlating the types of language disturbances generated by DES with the anatomical location of the stimulation probe. From these original data, we will show that the serial LRM model cannot explain all the symptoms elicited by DES, and we will propose an alternative hodotopical model of naming processing. Finally, we will consider interaction between language and "amodal" cognitive functions such as working memory and executive control.

2. Investigating the LRM model with DES

In this paragraph, we will discuss how intraoperative DES can contribute to the identification of the language subcomponents involved in a picture naming task. To this intent, we will correlate DES observations with the LRM model (Levelt et al., 1999). Within this framework, the successful achievement of a picture naming task results from a staged process. According to this theory, the timing of the different sub-processes could be estimated from chronometric experiments or from invasive electrophysiological recording (Sahin, Pinker, Cash, Schomer, & Halgren, 2009). Guided by this LRM model, a meta-analysis of fMRI data has been performed (Indefrey & Levelt, 2004), with the aim to infer the anatomical sites of each computational step. However, we have to underline that, although the temporal sequencing of the different subcomponents would suggest serially organized anatomical systems, several sites are activated for each stage, suggesting that each stage is itself performed by a distributed network. In other words, despite a temporal serial model, the spatial underlying architecture appears to be highly non-local (parallel).

Fig. 1 summarizes the correlations between the different types of errors observed when applying DES during a picture naming task and the LRM model, as follows: visual (formal) paraphasia, semantic paraphasia and anomia, morphological verbal paraphasia, phonemic paraphasia, phonetic paraphasia and articulatory disturbances.

First of all, if early visual object recognition is inhibited by DES, it will generate visual paraphasia, for example «cat» instead of «mask». Visual (formal) paraphasia is thus identified by the high degree of visual similarity shared by the target item and the selected one (Mandonnet, Gatignol, & Duffau, 2009).

Semantic paraphasia – for example «sheep» instead of «goat» – corresponds in the LRM model to a wrongly selected lemma. Moreover, within the LRM framework, the lemma selection results from a two steps process: conceptual encoding and lexical selection. For simplicity, we suggest to gather these two stages, by considering these processes as an amodal semantic computation – which in turn can influence the visual recognition by top-down processes (Kherif, Josse, & Price, 2011). Nonetheless, this model cannot explain the double dissociation between picture naming and comprehension, reported by several teams (Bello et al., 2007; Gatignol, Capelle, Le Bihan, & Duffau, 2004). Indeed, by confronting picture naming task and a semantic test of association (Pyramidal and Palm Tree Test, PPTT), DES over the posterior temporal lobe in the left dominant hemisphere elicited selective inability to name the word without comprehension deficit in discrete sites distinct from neighboring cortical areas inducing comprehension disturbances despite naming preservation (but with production of the wrongly selected item on PPTT) (Bello et al., 2007; Gatignol et al.,

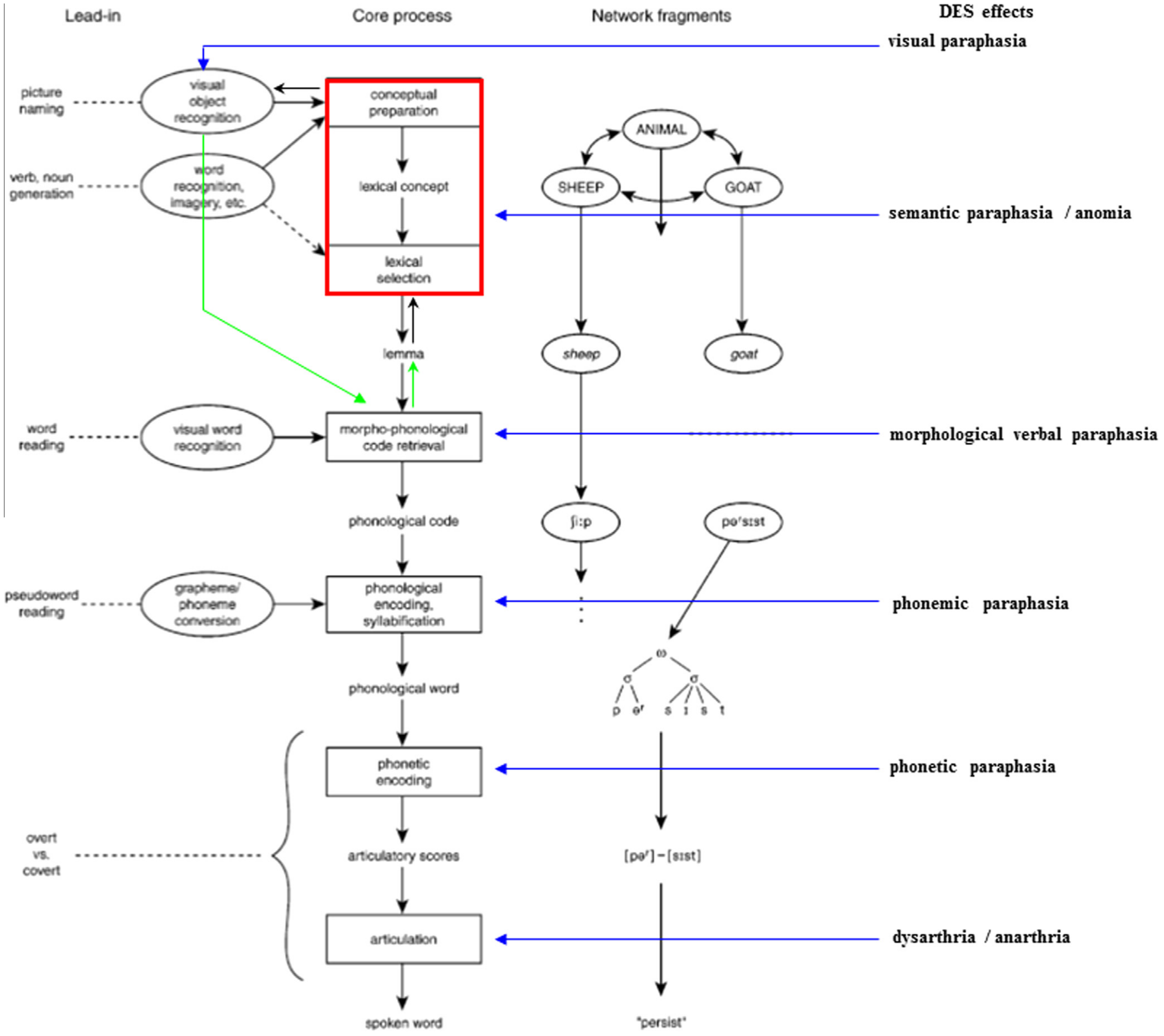

Fig. 1. Investigating the LRM model with intraoperative stimulation: correlations between the different types of errors observed when applying DES during a picture naming task and the LRM model. Green arrow: to explain double dissociation between picture naming disorders and comprehension disorders during DES, we propose to add a parallel pathway in the LRM model, making a direct connection between the visual object form and its phonological form, bypassing the semantic pathway.

2004). To explain such double dissociation, we propose to add a parallel pathway in the LRM model, making a direct connection between the visual object form and its phonological form, bypassing the semantic pathway. Of note, this suggestion has already been made in the past (Ferrand, 1997). Thanks to this direct association, the error in the retrieval of the morpho-phonological code, eliciting a morphological verbal paraphasia (for example «telephone» instead of «elephant»), can occur independently of any pre-selected lemma. From the binding of the visual object form and the phonological form, the amodal lemma will also be ultimately activated. Of note, anomia – that is, the inability to name the picture while being still able to say a short sentence as «this is ...» preceding the picture – may be viewed as an extreme case of semantic paraphasia. In this case, no lemma can be selected and/or the access to the phonological code is completely blocked.

Phonemic paraphasia during DES – for example «boat» instead of «goat» – can be interpreted as a failure of the phonological encoding step, while phonetic paraphasia would be caused by an error during the phonetic encoding. Speech arrest, a crucial symptom during awake mapping because enabling the selection of the optimal threshold with regard to the electrical intensity of stimulation (Duffau et al., 2008), is defined by a total impossibility to speak, while being still able to perform rapid alternating movements of the tongue (Matsumoto et al., 2004) (this last point allowing to make the distinction with a complete anarthria). Speech arrest would be a complete failure of the encoding stage. Finally, dysarthria (or anarthria at the extreme) arises as a jamming of the articulatory programs by DES.

It is worth noting that, up to now, all errors type elicited by DES have been analyzed as arising from an aborted computation devoted to a sub-function. However, errors could also be interpreted either as a jamming of the information itself or as a failure of its transfer between each stage, while computation «per se» would remain effective. To which extent information and computation are supported by separate neural systems (or not) in the brain remains a matter of debate. Our aim is now to bring new insights into this

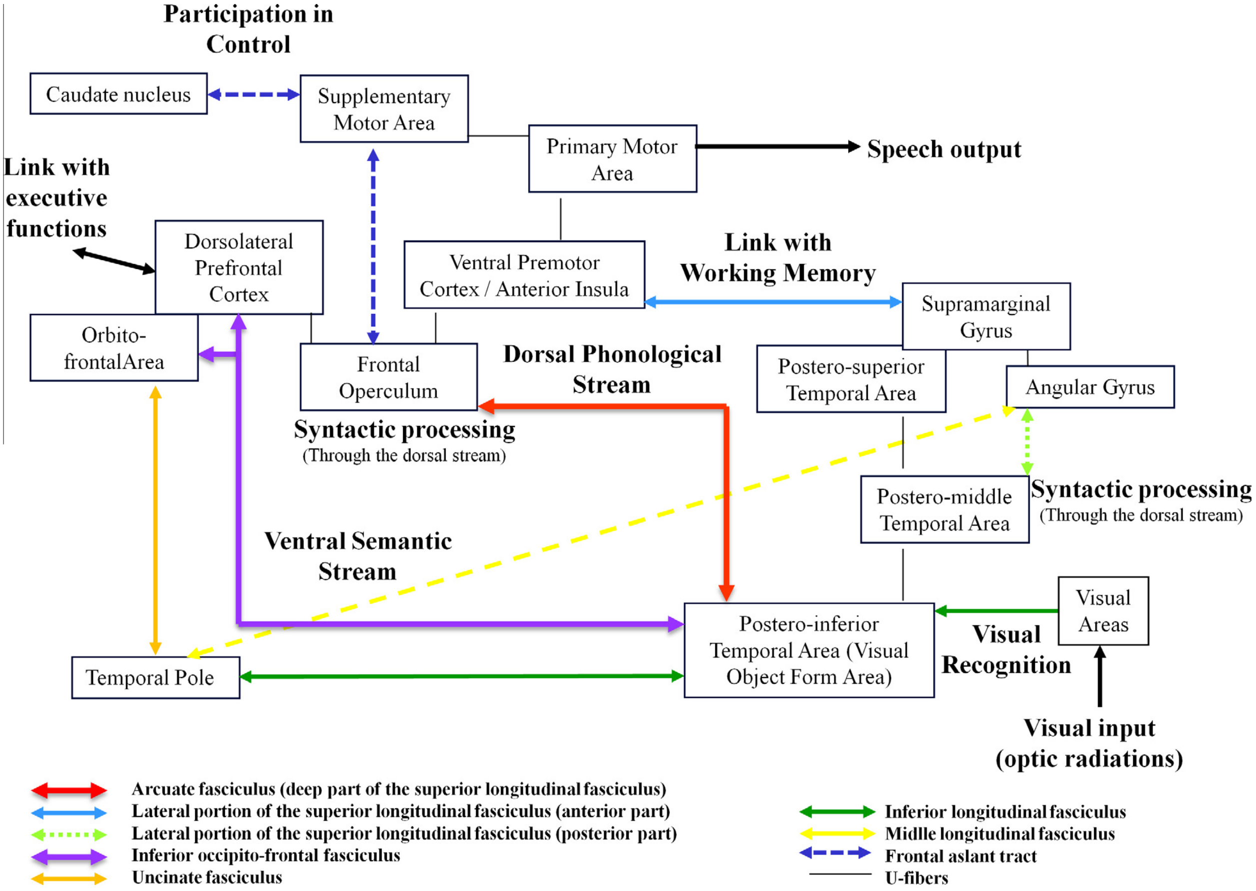

Fig. 2. Proposal of a hodotopical model of language, with incorporation of anatomic constraints, elaborated on the basis of structural–functional correlations provided by intraoperative DES.

controversy, on the basis of structural–functional correlations provided by cortical and subcortical DES. Indeed, due to the limitations of the serial LRM model (e.g. unable to explain double dissociation between picture naming and comprehension, as mentioned above), and which does not take into account anatomical constraints, especially concerning the axonal connectivity, which is crucial for both computation and transfer of information, we will propose a new hodotopical model of language organization with special emphasis on its neural foundations.

3. Anatomo-functional correlations provided by DES: shift towards a hodotopical model

3.1. Input: visual recognition

Subcortical DES of the optic radiations (Duffau, Velut, Mitchell, Gatignol, & Capelle, 2004) as well as cortical DES of the primary visual area (Nguyen, Sundaram, Mosier, & Cohen-Gadol, 2011) may elicit phosphenes (flashes) and/or reversible visual loss in the contralateral visual field reported by the awake patients, demonstrating an inhibition of the first stage of visual perception. Visual formal paraphasia has been generated by electrical interferences with a second stage of visual processing, that is, visual recognition (Mandonnet et al., 2009). We showed that these visual disturbances were induced by axonal DES of the posterior part of the indirect occipito-temporal system (inferior longitudinal fascicle), constituted by a succession of U-shape fibers (Catani, Jones, Donato, & ffytche, 2003), which links the visual cortex with the "visual object form area" (Mandonnet et al., 2009). This area, located within the basal occipito-temporal region, is involved in the first step of picture naming process, i.e. object recognition (Mandonnet et al., 2009). The visual object form area is near the visual word form area, which receives another subpart of the inferior longitudinal fascicle as afference, a sub-pathway involved in reading and generating alexia when damaged (Gaillard et al., 2006). In addition, by performing subcortical DES of distinct sub-components within the occipito-temporal white matter, it was possible to induce a double dissociation between alexia (lower fibers) and anomia (upper fibers) in the same patients (personal unpublished data). Therefore, these findings support the existence of parallel pathways coming from the occipital cortex, specifically involved in word versus object recognition.

3.2. The dual route: ventral semantic stream and dorsal phonological stream (Fig. 2)

Since the seminal work of Ungerleider and Haxby, the processing of visual information is divided in two principal streams: the ventral one, specialized in object identification (the "what" pathway) and the dorsal one, dedicated to the analysis of the spatial position (the "where" pathway) (Underleider & Haxby, 1994). Recently, built on an analogy between the visual and auditory systems, the following dual stream model for auditory language processing was suggested in humans: a ventral stream would be involved in mapping sound to meaning, and a dorsal stream in mapping sound to articulation (Hickok & Poeppel, 2007; Saur et al., 2008). Here, on the basis of functional disturbances induced by DES during picture naming, we will propose an original model for visual language processing in humans (after the first step of visual recognition): a ventral stream is involved in mapping visual information to meaning, and a dorsal stream in mapping visual information to articulation through visuo-phonological conversion. In our model, because double dissociation between phonemic and semantic processing has been elicited by DES (Maldonado et al., 2011a), we suggest that both processes are performed in parallel, and not serially.

3.2.1. Ventral semantic stream

Cortically, semantic paraphasias have been observed during intraoperative DES along the posterior part of superior temporal sulcus as well as in the frontal lobe, in the dorsolateral prefrontal cortex and in the pars orbitalis of the inferior frontal gyrus (Bello et al., 2007; Duffau et al., 2005). Axonally, such errors are elicited by DES of the white matter within the roof of the temporal horn of the ventricle, in the floor of the external/extreme capsule under the limen insulae, and more anteriorly at the level of the fibers connected to the dorso-lateral prefrontal cortex (Benzagmout, Gatignol, & Duffau, 2007; Duffau, Moritz-Gasser, & Gatignol, 2009; Duffau et al., 2005, 2008; Plaza, Gatignol, Cohen, Berger, & Duffau, 2008).

Interestingly, recent DTI studies have evidenced a ventral route connecting posterior temporal area and frontal area (Frey, Campbell, Pike, & Petrides, 2008; Makris et al., 2005; Parker et al., 2005; Saur et al., 2008). This ventral stream is now referred as «extreme capsule fiber system» with reference to connectivity studies in non-human primate. In our view, and as suggested by others (Karnath, Rennig, Johannsen, & Rorden, 2011; Parker et al., 2005; Turken & Dronkers, 2011), this system is conceptually the same as the inferior fronto-occipital fascicle (IFOF). Anatomically, even if it does not exist in monkeys, the IFOF has been first dissected in humans by Curran (1909), confirmed by Ludwing and Klingler (1956), Kier, Staib, Davis, and Bronen (2004), Fernandez-Miranda et al. (2008) and Martino, Brogna, Gil Robles, Vergani, and Duffau (2010a), as well as tracked using DTI by Catani et al. in 2002 – and then confirmed by all DTI studies but one (Makris & Pandya, 2009). We think it is more adapted to speak about IFOF rather than extreme capsule, because the latter only considers a discrete anatomical structure while the former considers an actual neural pathway with its cortical terminations, in a hodotopical view. Indeed, if one takes account of the sole white matter bundle without any considerations regarding the cortical epicenters connected by the fascicle, it does not allow the understanding of the network and its functional role. Interestingly, recent anatomic studies using a modified Klinger method with cortex-sparing fiber dissection (Martino et al., 2011) accurately analyzed not only the subcortical trajectory of the IFOF (Martino, Vergani, Gil Robes, & Duffau, 2010b) but also its posterior cortical terminations (Martino et al., 2010a). A basal occipito-temporal origin was identified, typically corresponding to the location of the visual object form area already described as involved in the previous step of visual recognition. In addition, a posterior cortical termination was also detected at the level of the posterior occipital lobe (Martino et al., 2010a). Of note, subcortical DES of white matter fibers situated deeply and above the inferior longitudinal fascicle (eliciting visual paraphasia, see above) can generate specific semantic paraphasia (unpublished personal data). Thus, the existence of a sub-part of the IFOF directly connecting the occipital cortex with the frontal lobe could be hypothesized. In addition, the anterior cortical terminations comprise the inferior frontal gyrus and the dorso-lateral prefrontal cortex, as revealed by DTI (Catani, Howard, Pajevic, & Jones, 2002) and fiber dissection (unpublished personal data). These areas are known to be involved in language semantics, as demonstrated using fMRI studies (for a meta-analysis, see Vigneau et al., 2006) as well as using cortical DES (Duffau et al., 2005). We will detail later that these areas are able to make the link with higher cognitive function such as plurimodal integration and judgment (Plaza et al., 2008). In our model, pretreated information by the visual recognition system is subsequently processed by the semantic system, in parallel to the dorsal phonological stream (see below), before being processed by the executive system.

In addition to this direct ventral route sub-served by the IFOF, an indirect ventral semantic pathway seems to exist, with a relay at the level of the temporal pole. Indeed, the temporal pole is considered as a "hub", that is, a functional epicenter allowing a plurimodal integration of the multiple data coming from the unimodal systems – explaining its role in semantics and its involvement in semantic dementia when (bilaterally) damaged (Holland & Lambon-Ralph, 2010). This indirect ventral stream is constituted by the anterior part of the inferior longitudinal fascicle, connecting the visual object form area with the temporal pole (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007), and then relayed by the uncinate fascicle which links the temporal pole with the pars orbitalis of the inferior frontal gyrus (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009). It is nonetheless worth noting that this indirect pathway can be functionally compensated when (unilaterally) damaged, as extensively demonstrated following anterior temporal lobectomy in epilepsy surgery (Duffau, Thiebaut de Schotten, & Mandonnet, 2008). Even if very mild and selective deficit may persist, as proper name retrieval (Papagno et al., 2011), this is a good illustration of "subcortical plasticity", in which a sub-network (IFOF, direct pathway) is able to bypass another sub-network (indirect pathway) and to functionally compensate it (Duffau, 2009). Finally, another pathway, the middle longitudinal fascicle, could also participate in the ventral semantic route (Saur et al., 2008). This bundle, which seems to connect the angular gyrus with the superior temporal gyrus up to the temporal pole, runs in the white matter within the superior temporal gyrus (Makris et al., 2009). Nonetheless, subcortical DES of this fascicle failed to induce any naming disorders (De Witt Hamer, Moritz-Gasser, Gatignol, & Duffau, 2011). Thus, its exact functional role is still unclear.

3.2.2. Dorsal phonological stream

Cortically, phonemic paraphasia induced by intraoperative cortical DES has scarcely been reported in the literature. A recent systematic analysis of naming errors during cortical stimulation mapping showed that, in contrast to semantic paraphasias, due to the rarity of phonemic paraphasia, no cortical region was significantly associated with this type of error (Corina et al., 2010). However, if in our experience we reported phonemic paraphasia by stimulating the inferior parietal lobule and the inferior frontal gyrus (Benzagmout et al., 2007; de Witt Hamer et al., 2011; Maldonado et al., 2011a), its low rate could be explained by the high frequency of speech arrest in the perisylvian fronto-parietal areas, preventing to verify whether phonological processing has been disturbed by DES due to the complete inhibition of output.

On the other hand, axonally speaking, several studies have observed phonemic paraphasia when stimulating the white matter all around the superior and posterior part of the superior insular sulcus (Bello et al., 2007; Benzagmout et al., 2007; de Witt Hamer et al., 2011; Duffau et al., 2008; Maldonado, Moritz-Gasser, & Duffau, 2011b; Maldonado et al., 2011a). Anatomically, this bundle corresponds to the arcuate fascicle (AF), which is a fiber tract stemming from the caudal part of the temporal lobe, mainly the inferior and middle temporal gyri, that arches around the insula and advances forward to end within the frontal lobe, essentially within the ventral premotor cortex and the pars opercularis of the inferior frontal gyrus – as demonstrated by fiber dissection (Fernandez-Miranda et al., 2008; Martino et al., 2011) as well as by several recent DTI studies (Bernal & Altman, 2010; Catani, Jones, & ffytche, 2005; Frey et al., 2008; Glasser & Rilling, 2008; Makris et al., 2005; Parker et al., 2005). With regard to functional aspects, Geschwind postulated that lesions of this tract would produce conduction aphasia, including phonemic paraphasia (Catani, Jones, & ffytche, 2005; Geschwind, 1970). Thus, the role of the sub-part of the dorsal stream mediated by the AF would be devoted to phonological processing (Parker et al., 2005), as supported by axonal DES data. Interestingly, the posterior cortical origin of the AF within the posterior part of the inferior temporal gyrus (Martino et al., 2011) seems to correspond to the visual object form area. Indeed, this region represents a functional hub, involved both in semantic (see above) and phonological processing, dedicated to visual material – as demonstrated in a functional MRI meta-analysis (Vigneau et al., 2006). Therefore, we postulate that phonological process sub-served by the AF is performed in parallel to the semantic process underlain by the ventral route (Mandonnet et al., 2009).

Of note, in addition to the direct dorsal route (AF), recent DTI studies evidenced the existence of an indirect dorsal stream, running more superficially, and underlain by the lateral superior longitudinal fascicle (Catani et al., 2005). This pathway will be analyzed in the next chapters, because it seems to be involved in other functions, that is, articulation and phonological working memory.

3.2.3. Double dissociation between semantic and phonological processing evidenced by DES

In our model, in contrast to the serial LRM model, pretreated information by the visual recognition/transformation system is subsequently processed by the ventral semantic system in parallel to the dorsal phonological stream before its integration and the output (see below). Such proposal is highly supported by double dissociations during subcortical DES.

Indeed, regarding the ventral route, although semantic paraphasia has systematically been generated by IFOF stimulation (whatever the part of the bundle stimulated, i.e. within the temporal lobe, under the limen insulae or in the frontal lobe), phonological paraphasia has never been elicited (de Witt Hamer et al., 2011; Duffau et al., 2005; Mandonnet et al., 2007). The interpretation is that ventral semantic stream allows interconnection between hubs, with a direct communication between the posterior temporal visual object form area and frontal plurimodal regions (Ius, Angelini, Thiebaut de Schotten, Mandonnet, & Duffau, 2011). Such an integration performed at the level of this wide network may lead to the conceptualization, independently of parallel processes performed by the dorsal phonological route. On the other hand, whereas phonological paraphasia has systematically been induced by AF stimulation (whatever the part of the bundle stimulated, i.e. within the posterior temporal lobe, under the inferior parietal gyrus or in the posterior frontal lobe), semantic paraphasia has never been observed (Maldonado et al., 2011b) – in agreement with the classical semeiology of "conduction aphasia" based on lesion studies. As a consequence, we recently suggested that the dorsal route does not participate in the semantic processing (Maldonado et al., 2011b).

Interestingly, an analogy can be made between the hodotopical/parallel organization of visual language processing here proposed and the dual route model described by Hickok and Poepple concerning auditory language processing (Hickok & Poeppel, 2007). According to their model, all sounds undergo spectral and phonological analyses in the dorsal superior temporal gyrus and posterior superior temporal sulcus. From this area, which can be considered as an analogous (for sound processing) to the visual object form area (for visual material), the processing of sounds diverges into a ventral route for auditory language comprehension and a dorsal route involved in auditory-motor transformation (Hickok & Poeppel, 2007). However, it is worth noting that Hickok and Poppoel took into account only the cortical areas, with no consideration regarding the subcortical white matter fibers – conversely to our model.

3.3. Output

Sites are thought to be involved in the articulatory system when their stimulation induces a transient dysarthria or a complete anarthria. These disturbances might be accompanied by mouth or facial movements, in contrast to speech arrest. Furthermore, the possibility to perform rapid alternating movements of the tongue characterizes rigorously speech arrest (Matsumoto et al., 2004), even if this testing is not systematically performed intraoperatively. According to these criteria, cortical areas eliciting articulatory disorders are located in the rolandic operculum, especially the ventral premotor cortex, in the ventral part of the supramarginal gyrus as well as in the posterior part of the superior temporal gyrus (Benzagmout et al., 2007; De Witt Hamer et al., 2011; Duffau et al., 2003). Interestingly, this organization was similarly observed in both hemispheres (Duffau, Leroy, & Gatignol, 2008).

Axonally, DES of the white matter in the fronto-parietal operculum, as well as under the supramarginal gyrus, laterally and ventrally to the AF, induces anarthria as well (Duffau, Gatignol, Denvil, Lopes, & Capelle, 2003; Maldonado et al., 2011a, 2011b).

Interestingly, a recent DTI study has evidenced the existence of an operculo-opercular component of the superior longitudinal fascicle. It has been named, by analogy with non-human primate studies "SLF III" by some authors (Makris et al., 2005), or anterior segment by others (Catani et al., 2005). In the latter study, a posterior component is also described, linking the posterior temporal areas to the inferior parietal lobule. These data have been confirmed by fiber dissections (Fernandez-Miranda et al., 2008; Martino et al., 2011). More precisely, it was demonstrated that the anterior horizontal segment connected the supramarginal gyrus as well as the posterior portion of the superior temporal gyrus with the frontal operculum, while the posterior vertical segment connected the posterior portion of the middle temporal gyrus with the angular gyrus (Martino et al., 2011).

On the basis of these data, we hypothesize that articulatory codes are stored in the fronto-parietal loop linking ventral premotor cortex and antero-ventral supramarginal gyrus through the SLF III. Delocalizing this articulatory information enables to perform different computations on each ends, mediated by the U-fibers around each epicenters. Anteriorly, the ventral premotor cortex receives afferences bringing the phonological and/or phonetic information to be translated into articulatory motor programs and efferences toward the primary motor area. Of note, direct insulo-opercular connections, also eliciting articulatory disturbances during DES (Benzagmout et al., 2007; Duffau et al., 2003), may link the ventral premotor cortex to the insula, itself involved in planning of articulation (Dronkers, 1996; Duffau et al., 2009). Posteriorly, the ventral supramarginal gyrus receives feedback information from somatosensory and auditory areas (in the parietal lobe and superior temporal gyrus, respectively). That would explain why DES induces dysarthria/anarthria when applied over these posterior regions. Moreover, this on-line auditory and somatosensory feedback is in accordance with a neural model of the control of speech movements (Guenther, Ghosh, & Tourville, 2006). Interestingly, this organization of articulatory motor programs seems to be bilaterally represented (Duffau, 2008).

4. Other language aspects and interaction with high-order cognitive functions

4.1. Syntax

Neural basis of syntactic processing is still debated. At the word level, grammatical gender is a feature present in many languages (e.g. Spanish, Portuguese, French, Italian, German, Dutch, Polish, Russian, ...). It is a property of nouns used in these languages to signify syntactic agreement, for instance between nouns and their determiners or nouns and adjectives (Comrie & Helm, 1997). In the serial LRM model, the abstract lexical representation (the "lemma") is connected to nodes representing the words syntactic properties, such as grammatical gender. As a consequence, because in this model the lemma stratum mediates between conceptual and phonological lexical information, it has been postulated that the phonological form of the target word became activated only after the corresponding lemma had been selected (Levelt et al., 1999). Therefore, the retrieval of syntactic information is necessary for the building of the morphological code. In this setting, we performed electrical mapping using a naming task preceded by a short sentence to read "ceci est ...", namely the French translation of "this is ...". Interestingly, the grammatical article was not written on the screen between the sentence and the picture. In French, the article determines the grammatical gender, but with no correlation between gender and the semantic or phonological characteristics of the noun.

Cortical DES elicited reproducible syntactic gender disturbances in the inferior frontal gyrus and in the posterior part of the middle temporal gyrus (Vidorreta, Garcia, Moritz-Gasser, & Duffau, 2011). Nonetheless, no naming disorders were generated during stimulation of the syntactic sites, while cortical areas inducing naming disturbances never elicited grammatical gender errors when stimulated. Furthermore, at the subcortical level, stimulation of the white matter lateral to the caudate nucleus induced gender errors with no naming disorders (Vidorreta et al., 2011). As a consequence, this double dissociation between syntactic gender and naming processing supports independent network model rather than serial theory. These DES mapping findings are in agreement with the model proposed by Caramazza and Miozzo, in which semantic representations can directly activate word forms, without assuming an intervening lemma code (Caramazza & Miozzo, 1997). Therefore, we hypothesize the existence of a distributed temporo-frontal cortico-subcortical sub-network which might selectively sub-serve syntactic processing, even if interconnected with parallel sub-circuits involved in semantic and phonological processing during naming.

4.2. Working memory

On the basis of the fronto-parietal articulatory loop previously described, we suggest the existence of strong relationships of this loop subserved by the lateral part of the superior longitudinal fascicle with a network underlying verbal working memory network. This is in accordance with Baddeley's model, in which the phonological processing is divided into a phonological store (involving the left supramarginal gyrus) and an articulatory rehearsal module that can revitalized memorized information (distributed rather over the left inferior frontal area and the ventral premotor cortex) (Baddeley, 2010; Paulesu, Frith, & Frackowiak, 1993). Indeed, since any words is a combination of basic phonemes, such a loop would allow the brain to store transiently the phonological information contained in a word or even in a sentence. Thus, this phonological working memory is an important aspect of the phonological system, and has been the subject of many fMRI studies. Interestingly, in a recent meta-analysis, phonological working memory has been associated with a fronto-parietal loop, linking the dorsal part of the pars triangularis to the dorsal part of the supramarginal gyrus (Vigneau et al., 2006), and supporting our hypothesis.

As a consequence, this loop is likely involved in repetition, which in essence needs to transitorily maintain the phonological information. Cortical DES over the posterior part of the superior temporal gyrus and over the supramarginal gyrus, i.e. the posterior cortical terminations of the lateral part of the superior longitudinal fascicle (Martino et al., 2011), may induce deficit in repetition (Quigg, Geldmacher, & Elias, 2006; Quigg and Fountain (1999)). These findings could explain why DES of the AF did not disturb repetition in our experience. Therefore, we hypothesize that conduction aphasia, classically associating phonemic paraphasia and repetition disorders following a lesion of the AF (Geshwindt, 1970) might in fact result from the combination of a lesion involving both the phonological dorsal stream underlain by the AF (which generates phonological disorders) and slightly more superficially the lateral part of the superior longitudinal fascicle (which generates repetition disorders due to a damage of the loop sub-serving the phonological working memory). This is in agreement with the fact that, clinically, it is currently well known that conduction aphasias form a heterogeneous group, likely because deep lesions are rarely located exactly at the same place, especially in stroke (Naeser, Palumbo, Helm-Estabrooks, Stiassny-Eder, & Albert, 1989).

4.3. Executive control

Language is a cognitive function, which cannot be dissociated from executive functions. This is supported by intraoperative DES data. Language switching is a good illustration of this concept. Indeed, although studies on bilingualism are abundant, cognitive processes and neural foundations of language switching received less attention. Recent DES findings showed that stimulation over the inferior frontal gyrus and postero-superior areas of the temporal lobe elicited reproducible involuntary language switching in awake patients performing picture naming (Moritz-Gasser & Duffau, 2009a). In addition, subcortical stimulation of the superior longitudinal fascicle also elicited the same functional consequences, interpreted as the result of a transient disconnection within a wide sub-circuit (Moritz-Gasser & Duffau, 2009a). On the basis of these original data, combined with behavioral and neuroimaging studies (not detailed here since beyond the scope of the present article), we have proposed a new model of language switching. According to this model, the switching process is sub-served by a large-scale cortico-subcortical network, which includes the language sub-circuit described above, controlled by an executive system (comprising the prefrontal cortex, anterior cingulum, and caudate nucleus) (Moritz-Gasser & Duffau, 2009b). Nonetheless, due to the strong relationships between these two components, it seems impossible to clearly dissociate both processing, that is, a pure language circuit versus a pure executive system.

In the same state of mind, subcortical DES of deep gray nuclei during picture naming may also modulate the functional response. For example, it has been reported that stimulation of the head of caudate nucleus generated perseveration, i.e., the repetition of the previous item while the next picture was shown to the patient (Gil Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005). This supports the involvement of the caudate in response selection and control. Indeed, learning of a new task first requires inhibition of a previous learned sequence. Therefore, we can assume that stimulation of the head of the caudate might inhibit the inhibitory role of this structure, resulting in reactivation of the neural circuit that participated to the naming of the previous picture, explaining the occurrence of perseveration (Gil Robles et al., 2005). Once again, it is probable that DES does not elicit selective disturbances of a specific language network, but that it interrupts a more general striato-cortical executive "amodal" loop controlling language, among other cognitive functions.

In this setting, the combination of symptoms called "frontal syndrome" was recently challenged, with an alternative hodotopical (interconnected) and plastic (dynamic) view in which it is possible to link "frontal symptoms" not only to a frontal lesion but also to a non-frontal damage (Duffau, 2011). Interestingly, such symptoms could also be due to a "striato-cortical" dysconnection, and not exclusively to a "cortico-cortical" dysconnection. However, from an anatomical point of view, even if the subcallosal fascicle has been suggested to make the link between the supplementary motor area, cingulum and head of the caudate (Naeser et al., 1989) – eliciting a transcortical motor syndrome when stimulated, by disrupting initiation (Duffau et al., 2002) – this bundle is still matter of controversy and needs to be validated by further dissection and DTI studies. In this way, using DTI, a connection between the supplementary motor area and the caudate as well as between the supplementary motor area and the pars opercularis of the inferior frontal gyrus was recently reported: frontal aslant tract (Thiebaut de Schotten, dell'Acqua, Valabregue, & Catani, 2012).

4.4. Plurimodal integration

As already mentioned, several brain areas (such as the temporal pole or the prefrontal region) can be considered as a hub, that is, a functional epicenter which enables a plurimodal integration of the multiple data resulting from the parallel processing performed by the unimodal systems. Such an integration may lead to a high-level conceptualization, as supported by transient inhibition of hub by DES, which can induce errors of judgment. Indeed, by using a cross-modal task combining simultaneous visual presentation of a picture and auditory presentation of a word spoken by a speech therapist (with congruent visual-verbal stimuli referred to the same item versus incongruent visual-verbal stimuli which differed either semantically or phonetically), DES of the dorso-lateral prefrontal cortex generated picture-word matching disturbances but no naming impairment. Moreover, the elicited errors exclusively appeared in incongruent and not in congruent conditions (Plaza et al., 2008). The dissociation observed between correct picture naming and disturbed cross-modal judgment shows that DES of the dorso-lateral prefrontal cortex can inhibit the simultaneous processing of visual-verbal information within the plurimodal hub (which integrates data previously processed by different channels of information) without disturbing the unimodal (visual) network specifically involved in picture naming.

As a consequence, we hypothesize the existence of close interactions but also a certain degree of independency between the circuit underlying picture naming (itself constituted by parallel sub-networks involved in semantic, phonological and syntactic processing, as detailed above), amodal circuits involved in control, attention and working memory (able to select and maintain different kinds of information in the mental imaging, whatever the modalities), and plurimodal systems enabling to move towards a supramodal integration - which can finally lead to a higher level of conceptualization and then to decision-making.

4.5. Perspectives: emotional and behavioral aspects?

Although relationships between language and cognition have been more extensively studied in the past decades, emotional and behavioral considerations have received less attention. However, neural correlates of sites/networks binding function of emotional information with language begin to be investigated, essentially using functional MRI (Willems, Clevis, & Hagoort, 2011). Interestingly, the right hemisphere seems to play a pivotal role in para-linguistic processes such as the processing of emotional prosodic information (Beaucousin et al., 2007) and integration of context (Vigneau et al., 2011) to construct a complete representation of meaning and intent. Cortical and axonal DES were also used to map the right hemisphere with regard to language in left-handers and ambidextrous (Duffau et al., 2008) as well as in right-handers (Vassal, Le Bars, Moritz-Gasser, Menjot, & Duffau, 2010). They revealed a mirror organization of the language networks in comparison with the left hemisphere. Furthermore, a recent stimulation study investigated more specifically the neural basis underlying recognition of facial emotions, and showed the involvement of the right posterior perisylvian area (Giussani, Pirillo, & Roux, 2010). Since awake surgery for non-language mapping has been proposed in addition to the classical language investigation (Duffau, 2010), the precise interactions between language (not only semantics, phonology and syntax but also its pragmatic) and behavioral aspects (such as theory of mind, empathy, or spatial cognition) will probably benefit from more regular and specific studies in the near future.

5. Conclusions

On the basis of original data provided by intrasurgical DES in awake patients, we propose a hodotopical and dynamic model of visual language processing, which breaks not only with a localisationist view but also with the serial LRM model. Due to its organization in parallel, segregated (even if interconnected) large-scale and delocalized cortico-subcortical sub-networks underlying semantic, phonological and syntactic processing, our model offers several advantages:

- it is able to explain double dissociations regularly observed in lesion studies (including DES investigation) at different levels: dissociation between comprehension and picture naming disorders, dissociation between semantic and phonemic paraphasia, dissociation between syntactic and naming disturbances, dissociation between plurimodal (visual-auditory) integration and naming disorders;
- it takes into account the anatomic constraints both at cortical and axonal levels, which is a crucial point – because a model is not completely validated without the confirmation of its neural foundations using reliable anatomo-functional correlations;
- it explains the mechanisms of compensation underlying brain plasticity and recovery of aphasia following a permanent lesion (not transient DES) within the "classical" language areas according to traditional models. Indeed, preservation of direct pathways sub-serving the subcortical connectivity (e.g. the IFOF or AF) may allow the continuation of language processing thanks to the spared communication between the distributed cortical epicenters, despite the damage of one (or several) of them. This was well illustrated by complete language restoration after surgical resection of Broca's area (Benzagmout et al., 2007; Plaza, Gatignol, Leroy, & Duffau, 2009), of the whole left frontal lobe without any language or "frontal" deficits (Duffau, 2012), of the left inferior parietal lobule (Maldonado et al., 2011a) or even of the left temporal lobe (Duffau, 2005) including Wernicke's area (Sarubbo, Le Bars, Moritz-Gasser, & Duffau, 2012). Indeed, a recent probabilistic map defining the "minimal common brain" has confirmed that cerebral plastic potential was significantly lower at the axonal level compared with the cortical structures (Ius et al., 2011);
- finally, this model establishes links with amodal cognitive functions such as working memory and executive control.

As a consequence, this model may have important fundamental as well as clinical implications (e.g., in brain surgery, for prediction of recovery of aphasia in neurological diseases, for the planning of individualized programs of language and cognitive rehabilitation). Implementation of this model will nonetheless be necessary, especially with regard to the emotional and behavioral aspects.

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