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New insights into the neural foundations mediating movement/language interactions gained from intrasurgical direct electrostimulations

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ABSTRACT

Interactions between language and motricity have been a topic of interest in brain development as well as in pathological models. The role of the motor system in language has been investigated through neuroimaging and non-invasive brain stimulation methods. However, little is known about the neural basis that might be involved in such interactions. Meanwhile, brain direct electrostimulations (DES) have provided essential knowledges about the connectomic organization of both motor and language systems. We propose here to review the literature about DES from the outlook of interactions between language and motricity and to investigate common cortico-subcortical structures shared by both networks. Then we will report an experimental study about the spatial distribution of DES eliciting simultaneous speech and contralateral upper limb negative motor response in a series of 100 patients operated on under awake condition for a low-grade glioma. From the probabilistic map obtained, a structural connectivity analysis was performed to reveal the cortico-subcortical networks involved in language and motricity interactions. The embodiment suggested by these results takes place in parallel and distributed bilateral fronto-temporo-parietal networks rather than in a single and somatopically well defined organization as previously suggested.

1. Introduction

Neural foundations of language and motricity have been largely studied in neurosciences given the serious consequences in term of autonomy and quality of life after brain injury. Beyond that, some studies have tried to identify the functional link between language and motor activity in order to find how one function could influence the other (De Stefani & De Marco, 2019; Dreyer & Pulvermüller, 2018; Pérez-Gay Juárez, Labrecque, & Frak, 2019). Many methods have been employed to assess this link, especially structural and functional imaging. However, these studies lacked direct investigation on the human brain. Such investigations can be provided by direct electrostimulations (DES) to map cortical and subcortical functional structures as demonstrated with the Penfieldian Homunculus for motor function (Penfield & Boldrey, 1937). DES have been widely used during brain surgery to map motricity and language, providing in return many findings regarding their connectomic organization (Duffau, 2001, 2015; Herbet & Duffau, 2020; Mandonnet, Winkler, & Duffau, 2010; Tate, Herbet, Moritz-Gasser, Tate, & Duffau, 2014). Nevertheless, DES have only been used to explore separately language and motor activity, without focusing on potential interaction or on dual responses, namely language and motor disorders during a single electrostimulation. Our objective in the first part is to highlight results from DES studies reporting functional and structural relationship between language and motricity and to look how they can lead to new hypotheses about interaction between language and movement. In a second part we will

Abbreviations: AF, arcuate fascicle; AG, angular gyrus; DES, direct electrostimulations; DNMR, Dual negative motor response; FAT, frontal aslant tract; FST, fronto-striatal tract; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fascicle; ILF, inferior longitudinal fascicle; M1, primary motor cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; NMR, negative motor response; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PMR, positive motor response; PreCG, precentral gyrus; PostCG, postcentral gyrus; SFG, superior frontal gyrus; SLF, superior longitudinal fascicle; SMG, supramarginal gyrus; STG, superior temporal gyrus; SA, speech arrest; SMA, supplementary motor area; UL, upper limb

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report an original work about the spatial distribution and structural connectivity of cortical sites harboring simultaneous speech and motor disturbances during a single DES in a series of 117 patients operated on under awake conditions for a low-grade glioma. These results will be compared to current hypotheses and knowledge about the organization of speech and motor networks and how these functions can influence each other.

1.1. Principle of direct electrostimulations

DES consist in applying an electric current onto the brain to create a virtual and transient lesion of the cortical or subcortical structures stimulated while the patient is performing a cognitive or motor task and thus to inform the surgeon about the functional consequence if this structure was removed. They have been widely used for several decades during awake surgery for tumor removal or epileptic surgery, every time a pathologic, indiscernible and infiltrative tissue requires to be removed from the brain while preserving brain functions.

DES are performed thanks to a bipolar electrode (tip to tip distance varying from 5 to 10 mm) which delivers a biphasic current (60 Hz, duration of 1 ms, amplitude range from 1 to 10 mA) (Mandonnet et al., 2010). It is then possible to map a function such as language or motricity at the level of the cortex and to continue the mapping by following the white matter pathways emerging from these cortical areas. This subcortical mapping is of great interest to validate the cortical mapping and avoid false positive due to partial seizure or current spreading. Sometimes, DES are delivered extra-operatively, namely after placing subdural electrodes grids and then performing the functional assessment to the patient's bed. This is of importance as it explains difference between studies where several cognitive tests with repetitive stimulations can be performed in extraoperative conditions while brain mapping during awake surgery is time - and then task – limited (Duffau, 2013). In all cases, the cognitive and motor assessments are performed throughout the mapping by a neuropsychologist and/or a speech therapist who reports functional disorders such as anarthria, anomia, paraphasia, muscle contraction or movement arrest.

DES during awake surgery are considered as the gold standard for brain mapping given its high sensibility and reliability (De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012). They present a very low rate of false negative – provided a rigorous methodology - and act as an input gate into functional network, explaining why the same symptom can be elicited on different structures of the network, namely cortical or subcortical ones (Mandonnet et al., 2010). This exploration of brain networks provides many information about the connectomic organization of the brain in many fields of neurosciences (Herbet & Duffau, 2020), especially because it is possible to collect the MNI coordinates of the functional cortical and subcortical sites after plotting them on the normalized postoperative MRI of the patient. This methodology has allowed neuroscientists to create probabilistic map of functional networks (Sarubbo et al., 2020) as well as plasticity map of the brain (Herbet, Maheu, Costi, Lafargue, & Duffau, 2016). Nevertheless, despite a growing interest in neuroscience DES has almost be used only to analyze each function separately.

1.2. Motor mapping

Historically, Penfield described firstly the distribution of motor and somesthesic areas with the classical Penfieldian homunculus (Penfield & Boldrey, 1937). At this time, motor mapping was quite simple as the assessment consisted in looking for muscle contraction during stimulation, defined as positive motor responses (PMR). This protocol of mapping allowed the surgeon to prevent the occurrence of permanent motor deficit. Since then, several studies reported motor mapping at a cortical and a subcortical level, during awake surgery but also under general anesthesia as motor function can also be monitored through electrophysiological strategy by assessing motor evoked potential (Bello et al., 2014). PMR were reported all over the primary motor cortex (M1) with a somatotopic distribution (Penfield & Boldrey, 1937). Then, successive studies reported a larger area of distribution of PMR, over the precentral gyrus (preCG) (Duffau, 2001; Enatsu et al., 2013; Matsumoto et al., 2006; Tate et al., 2014) and beyond, over the superior (SFG) and middle frontal gyrus (MFG) (Borggraefe et al., 2016; Nii, Uematsu, Lesser, & Gordon, 1996), extended then the area of PMR from M1 to the premotor cortex. At the subcortical level, the pyramidal tract requires also to be identified thanks to PMR (Duffau et al., 2003) as brain lesions such as glioma often infiltrate the white matter pathways (Mandonnet, Capelle, & Duffau, 2006). On the medial face of the hemisphere, stimulations over the paracentral lobule as well as the supplementary motor area (SMA) can evoke PMR (Trevisi et al., 2018). Single or complex movement of one limb or the whole contralateral hemibody and sometimes of the ipsilateral or bilateral sides are possible by stimulating the SMA and a broad somatotopic distribution can be found with lower limb, upper limb and head by starting from the paracentral lobule and going postero-anteriorly (Fried et al., 1991; Lim et al., 1994; Matsumoto et al., 2006).

Nevertheless, despite this positive cortico-subcortical motor mapping, it was not possible to prevent the occurrence of the SMA syndrome, defined by a complete contralateral akinesia of the hemibody and a mutism in the dominant hemisphere. This syndrome, considered as totally reversible, is in fact followed by permanent deficit in the fine motors skills and bimanual coordination even if the patient was operated on under awake condition with a correct positive motor mapping (Duffau, Lopes, Denvil, & Capelle, 2001; Krainik et al., 2004; Laplane, Talairach, Meininger, Bancaud, & Orgogozo, 1977; Zentner, Hufnagel, Pechstein, Wolf, & Schramm, 1996). However, recent advances in motor mapping have shed the light on a phenomenon called negative motor response (NMR) which corresponds to a complete arrest of movement without loss of tone or consciousness after an electrical stimulation (Lüders, Lesser, Morris, & Dinner, 1987). This NMR can involve the limbs but also the face and speech. The recent description of NMR at a subcortical level has helped to reveal a large cortico-subcortical network able to modulate the motor control. Cortical sites harboring NMR are localized over the preCG, the SMA and more rarely over the postcentral gyrus (postCG) (Borggraefe et al., 2016; Enatsu et al., 2013; Filevich, Kühn, & Haggard, 2012; Mikuni et al., 2006; Rech et al., 2019; Trevisi et al., 2018). The subcortical pathways driving these NMR have also been identified, especially the frontal aslant tract (FAT) and the fronto-striatal tract (FST). The FAT connects the SMA to the inferior frontal gyrus (IFG) and the ventral premotor cortex (PMv) (Catani et al., 2012) whereas the FST connects premotor areas to the striatum (Leh, Ptito, Chakravarty, & Strafella, 2007). Besides, DES of these tracts have shown a somatotopic distribution, with face/speech, upper limb, and lower limb NMR distributed from an anterior, ventral and lateral position to a posterior, dorsal and medial one, respectively. This somatotopic distribution pleads for a well-defined organization of the fibers involved in the motor control network. Site harboring bilateral NMR of upper limbs are located between contralateral upper limb NMR (Kinoshita et al., 2015; Rech et al., 2014, 2015; Schucht, Moritz-Gasser, Herbet, Raabe, & Duffau, 2013). In addition, DES of parieto-frontal fibers have also shown the possibility to elicit NMR (Almairac, Herbet, Moritz-Gasser, & Duffau, 2014). Interestingly, preservation of the NMR sites, and especially of the subcortical sites, does not lead to a SMA syndrome and its subsequent deficit whereas removing such sites is followed by permanent deficit in bimanual coordination and fine movement skills (Rech et al., 2017). This is in favor of an involvement of the negative motor network in motor control and that preservation of the motricity requires to take account of large cortico-subcortical network beyond M1. Consequently, each time the motor control network has to be preserved and whatever the hemisphere, it is recommended to perform a motor mapping under awake condition by asking the patient to perform contralateral flexion and extension of the upper limb at 0.5 Hz (i.e one flexion/extension cycle

every 2 sec) while performing the language task simultaneously and by looking for NMR as described previously (Rech et al., 2019).

1.3. Language mapping

One major reason to perform brain mapping under awake condition was the necessity to identify language areas during tumor resection (Berger & Ojemann, 1992; Duffau et al., 1999). Indeed, because of inter-individual variability and brain plasticity, cortical eloquent sites for language cannot be anticipated prior to surgery and require to be monitored on-line during the resection (Duffau, Denvil, & Capelle, 2002; Sanai, Mirzadeh, & Berger, 2008). Cortical areas responsible of anomia, semantic and phonologic paraphasias are localized over the IFG and MFG, the superior (STG) and middle (MTG) temporal gyri, the supramarginal (SMG) and angular (AG) gyri of the left hemisphere, namely far beyond Wernicke's area. Speech arrest are elicited over the PMv bilaterally and not over the classical Broca's area. Articulatory disorders can be induced by stimulating the preCG and postCG (Rech et al., 2019; Sanai et al., 2008; Tate et al., 2014). On the medial wall of the hemisphere, speech arrest, hesitation, slowdown of speech or vocalizations can be elicited on the SMA, more anteriorly than upper limb motor disturbances in a given patient, at the junction between the preSMA and the SMAproper (Borggraefe et al., 2016; Fried et al., 1991; Lim et al., 1994; Trevisi et al., 2018).

As for the motor system, identification of subcortical fibers is crucial as white matter plasticity remains limited compared to cortical one and constitutes a boundary during surgery (Duffau et al., 2002; Duffau, 2015, 2016; Herbet et al., 2016; Ius, Angelini, Thiebaut de Schotten, Mandonnet, & Duffau, 2011). It is possible to identify the dorsal phonologic pathway subserved by the arcuate fascicle (AF), connecting postero-inferior temporal structures to the IFG and the preCG, and the articulatory loop subserved by the superior longitudinal fascicle III (SLF III), connecting the posterior temporal structures and the SMG to the preCG. Stimulation of the AF induces phonemic paraphasia and repetition disorders while stimulations of the SLF III induce anarthria (Duffau, Moritz-Gasser, & Mandonnet, 2014). The ventral pathway is constituted by the inferior-fronto-occipital fascicle (IFOF) connecting the occipital and posterior temporal structures to the frontal lobe, especially the IFG and the dorso-lateral prefrontal cortex (DLPFC). An indirect ventral pathway is also constituted by the uncinate fascicle and the inferior longitudinal fascicle (ILF). DES of the IFOF generate semantic paraphasia in the left hemisphere and non-verbal semantic errors in the right hemisphere while DES of the ILF generate anomia if the temporal lobe is not damaged by the lesion (Herbet, Moritz-Gasser, Lemaitre, Almairac, & Duffau, 2018; Moritz-Gasser, Herbet, & Duffau, 2013). Stimulation of the FAT induces speech arrest or acceleration/slowdown of the counting, confirming its role in speech initiation and verbal fluency (Kinoshita et al., 2015).

As DES can induce language disorders in the left and right hemispheres, it is recommended to awaken the patient to perform verbal and non-verbal semantic task as well as denomination task thanks to the PPTT (pyramid and palm tree test) and the DO80 respectively.

2. Interaction between motricity and language during cortical and subcortical DES

2.1. Supplementary motor area

The SMA is classically considered as constituted by the preSMA, rostrally, and the SMA proper, caudally and anterior to the paracentral lobule. They are considered to play different role despite evidences suggesting that no discrete modules exist but rather a continuum from cognitive aspects devoted to the preSMA to more motor one allocated to the SMAproper (Geyer, Matelli, Luppino, & Zilles, 2000; Nachev, Kennard, & Husain, 2008). A somatotopy and rostro-caudal organization of language and motricity can be identified thanks to DES at the individual level but no sharpened border could be demonstrated on large sample of patients confirming this notion of continuum. Interestingly, it is not rare to elicit both speech and motor responses during cortical stimulation (Fried et al., 1991). It has also been shown that stimulation of the preSMA could lead to anomia without motor disturbance. Consequently, the preSMA could be involved in the lexico-semantic system, especially through its connection to the MFG and IFG whereas the SMAproper, connected to motor area and particularly to the PMv, would be more involved in speech production (Corrivetti et al., 2019). These results highlight the close relationship and possible interactions between motor and language networks at the level of the SMA. Indeed, given the difficulty to find module inside the SMA complex, one can assume that language and motricity – beyond the speech production - are processed at the same time by the same structure, underlying here the role of the SMA in the temporal aspect of behavior (Schwartze, Rothermich, & Kotz, 2012). This would be in accordance with the affordance theory in which a competition can occur between two behaviors - speaking vs moving in this case - (Pezzulo & Cisek, 2016) but also with hypothesis considering their processing by the same communication system in order to harmonize gesture and speech in the framework of verbal and nonverbal communication (Bernardis & Gentilucci, 2006).

2.2. Lateral face of the hemisphere

Recent DES study about NMR confirms the segregation of the premotor cortex previously reported with neuroimaging (Rech et al., 2019; Schubotz, Anwander, Knösche, von Cramon, & Tittgemeyer, 2010). Indeed, NMR were only found on the preCG, namely the PMd proper and the PMv (Genon et al., 2016; Picard & Strick, 2001) which could at least be divided up to 4 parts according to clusters of upper limb NMR. Such a segregation could also be done for speech NMR by identifying at least 2 clusters over the preCG on both hemispheres. Interestingly, clusters of speech NMR were distributed widely over the preCG, and especially far from Broca's area. This confirms the role of large portion of the premotor cortex in speech in both hemispheres. Moreover, those two clusters likely have different functions according to previous segregation of the preCG based on functional imaging (Glasser et al., 2016). It is therefore possible to show that the distribution of speech and upper limb NMR does not respect a somatotopic map as usually considered but is rather constituted by multiple and redundant subareas whose distribution is likely dependent on the task required in a "like attracts like" manner (Graziano & Aflalo, 2007). This organization could correspond to the one observed in area of the medial wall of the hemisphere, but the difference lies in the fact that multiple subareas could be identified. This seems that multiple processes involved in speech and motor activity occur at the level of the preCG.

Besides, clusters of speech and upper limb NMR are not just close together but seem to overlap. One can assume that this is an artificial view because the two probabilistic maps present large interindividual variability and therefore extend widely away from the maximum probability area. If this was the case, sites eliciting speech and upper limb NMR would be always separated at the individual level. However, results coming from this present study will show that numerous sites of NMR present dual responses for speech and upper limb. As a consequence, clusters of speech and upper limb are really sometimes overlapping, and these specific areas of dual NMR are taking in charge both speech and motricity. A deeper analysis of these results will be presented in the experimental part below.

2.3. White matter pathways

Stimulations of the FAT and FST can elicit both speech arrest and upper limb NMR probably because fibers supporting language and motor activity are so close together that they can be stimulated in the same place. It is also possible that one fiber/tract subserves both

functions. Consequently, these fibers likely arise from the same cortical origin or are going to the same target, for example the basal ganglia. These results are in accordance with findings concerning the cortical origin from which these fascicles are coming. Indeed, the FAT connects the SMA to the PMv, both areas involved in motor initiation and speech. The FST is connected to the basal ganglia and can be involved in the cortico-basal ganglia – cortical loop responsible of behavioral selection (Mandonnet et al., 2019). Subcortical stimulations have also confirmed the gradient between lexico-semantic system more rostrally and depending on the anterior portion of the FAT and FST, and speech-motor system caudally subserved by posterior portion of the FAT/FST (Corrivetti et al., 2019). Taken together, these findings suggest that language and motor control is distributed widely through the frontal lobe and subserved by a same multimodal cortico-subcortical network.

3. Direct electrostimulations to reveal interactions between speech and upper limb motricity: An experimental study

3.1. Context

As described in Section 2.2, clusters of speech and upper limb NMR are partially overlapping over the preCG. One remaining issue from the studies is that comparison between clusters has been done from a functional point of view but not by taking account of the structural connectivity. Moreover, this work (Rech et al., 2019) did not explore the specific phenomenon of dual NMR (DNMR) with simultaneous arrest of speech and upper limb during DES. Given previous hypothesis concerning interactions between motor and language activity (De Stefani & De Marco, 2019; Dreyer & Pulvermüller, 2018), we decided to focus on these DNMR sites and study their spatial distribution as well as their structural connectivity to investigate the cortico-subcortical basis of language and movement interaction.

3.2. Material and methods

3.2.1. Population and data collection

We collected data obtained from our previous work about the probabilistic map of NMR over the preCG where the precise methodology (i.e the protocol of cortical mapping and data extraction) is detailed (Rech et al., 2019).

All patients were adult and treated for a low-grade glioma. They were all operated on under awake conditions with functional brain mapping. Informed consent was obtained before surgery.

A language and motor assessment was performed during the cortico-subcortical mapping. Patient was performing an object naming task (DO 80) (Metz-Lutz, Kremin, & Deloche, 1991) at the same time with a motor task. This motor task included alternative flexion and extension of the contralateral upper limb at 0.5 Hz frequency (i.e. one flexion–extension cycle every 2 s). A site was considered functional if the stimulation led to an impairment followed by a normalization of the behavior at the cessation of the stimulation, three times in a non-sequential manner. A DNMR site was defined by a speech arrest and a NMR of the contralateral upper limb at the same time. MNI coordinates of DNMR sites were registered thanks to the postoperative MRI and an intraoperative photograph. A 5 mm-spherical volume of interest was created in MRIcron software and plotted over the ICBM 152 asymmetrical template to create probabilistic maps as previously described (Herbet et al., 2016; Mandonnet et al., 2007; Rech et al., 2019). Maps were then visualized in MRIcroGL software for 3D-rendering.

3.2.2. Data analysis

To perform the structural connectivity analysis, clusters obtained from our previous works were used as seeds (Rech et al., 2019). Indeed, these results rely on a large sample of stimulation sites and provide currently the best segregation of the preCG based on DES. Consequently, we used 3 clusters on the left hemisphere and 2 on the right.

Structural connectivity for each voxel in the whole brain was computed in each individual space from diffusion MRI data following the same pipeline as in Chen et al. (2019). We used a set of 467 subject from the Human Connection Project 1200 subject set, selecting every subject between 26 and 35 years old, with available DWI data. For each surface vertex in the grey-white matter interface, the cortico-cortical connectivity through probabilistic tractography was computed using a constrained spherical deconvolution model of within-voxel diffusivity (Jeurissen, Leemans, Jones, Tournier, & Sijbers, 2011). These techniques have been shown to improve the ability to track crossing and fanning fibers, however forking fibers continue to represent a methodological challenge using current diffusion MRI techniques. We also employed well-established method to correct for tract distance (Anwander et al., 2007). The FreeSurfer-obtained white matter surface was shrunk 3 mm into the white matter to avoid superficial tracts and was then seeded 5000 streamlines per vertex (Thomas et al., 2014). The proportion of streamlines connecting two vertices was interpreted as the probability that a white matter axonal bundle connects both cortical points, namely tract strength (Behrens et al., 2003). The decision to use 5000 streamlines as the number of trials was based on pilot studies and the observation that tract strengths stabilizes at this trial number across a holdout sample of vertices and participants. To assess population-wise connectivity of each one of the stimulation sites, we first calculated the probability of all cortico-cortical connections at the vertex level for each subject, estimated the 95-percentile value of the probability of all connections for the subject, and computed the median value across participants (0.00402). We then used this population median to threshold the probabilistic tractography maps. Plainly, we considered enough evidence for the existence of a white matter connection between a region and a cortical point, when a particle leaving the region has a probability of reaching the cortical point larger than this threshold.

3.3. Results

3.3.1. Distribution of dual NMR sites

117 patients presenting at least one NMR were included in the study. Among these patients, DNMR were found in 47 patients on the right hemisphere and 53 patients on the left one. Table 1 show demographic data about patients and tumors.

On the right hemisphere, DNMR were located over a large surface of the preCG (Fig. 1). One site was located on the dorsal bank of the post central gyrus and another over the caudal part of the SFG. Areas which presented the higher probability were located on the lateral part of the preCG, between the limit of the sylvian fissure and the superior frontal sulcus. The dorsal part of the preCG, above the limit of the superior frontal sulcus, did not harbor any DNMR.

On the left hemisphere, DNMR were identified at the same location over the lateral part of the preCG than on the right hemisphere (Fig. 1). Again, the most dorsal part of the preCG, just caudally to the SFG, was not involved. Three sites generated DNMR on the postCG, caudally to hand knob whereas two others elicited DNMR on the ventral part of the postCG. One single site generated a DNMR over the pars opercularis.

3.3.2. Structural connectivity

Fig. 2 shows the structural connectivity of each cluster. On the right hemisphere, the ventral (Fig. 2A) and the dorsal (Fig. 2B) clusters were connected ipsilaterally to large portion of the frontal, temporal and parietal lobes. However, some differences could be identified. The dorsal cluster was more widely connected with the SFG, MFG and IFG, beyond the limit of the premotor cortex. Contrary to the ventral cluster, it was also connected to the superior parietal lobule but did not show any connection with the SMG. Moreover, connections with the MTG and ITG were less numerous for the dorsal cluster. The dorsal cluster was connected widely with the preCG of the contralateral side whereas the ventral one harbored fewer connections and especially no

Table 1
Demographic data.

Population	
Patients (n)	100
Age (years)	39 ± 10
Male: female ratio	0,92
Handedness	
Right	85%
Left	12%
Ambidextrous	3%
Tumor side	
Right	47%
Left	53%
Tumor location	
Superior frontal gyrus	22%
Middle frontal gyrus	18%
Inferior frontal gyrus	9%
Anterior cingulate gyrus	5%
Frontobasal and frontopolar regions	33%
Precentral gyrus	5%
Postcentral gyrus	6%
Temporal pole	31%
Superior temporal gyrus	7%
Middle temporal gyrus	6%
Inferior temporal gyrus	6%
Temporo-occipital junction	1%
Hippocampus	7%
Superior parietal lobule	3%
Inferior parietal lobule	9%
Insula	37%

connection with the PMv.

On the left hemisphere, the three clusters showed also a large pattern of connection with the frontal, temporal and parietal lobes. Nevertheless, some differences appeared between ipsi and contralateral clusters. Indeed, ventral cluster (Fig. 2C) harbored the wider connections with the temporal lobe, including anterior part of the STG, MTG and ITG. Connections with the frontal lobe were larger than for the right side, extended rostrally up to the DLPFC. Moreover, this ventral cluster had wider connections with both preSMA than the other clusters. The dorsal cluster (Fig. 2D) showed almost the same connections as the right side with lesser extension over the frontal lobe. Finally, the third cluster (Fig. 2E), located on area 55b from Glasser's parcellation map (Glasser et al., 2016), presented a mixed pattern of connection. In fact, it had connections with the superior parietal lobule and contralateral preCG, as for the dorsal cluster but also large connections with the MTG, ITG and inferior parietal lobule, as for the ventral cluster.

3.4. Discussion

In this study we confirmed that the overlapping of map concerning speech arrest and upper limb NMR is not artefactual but corresponds to original dual responses elicited by DES. We provide here unique data reporting cortical areas whose stimulation can interfere with both speech and movement. DNMR seems to be a frequent phenomenon as it was found in 100 patients of our previous series. DNMR over the PMd (Fig. 2B and D) are in accordance with previous findings showing activation of dorsal premotor areas during language tasks in fMRI and suggesting a link between the semantic representation and the motor system (Boulenger, Hauk, & Pulvermuller, 2009; Hauk, Johnsrude, & Pulvermüller, 2004; Pulvermüller & Fadiga, 2010). Interestingly, it was also possible to elicit DNMR involving speech and upper limb at the level of the PMv (Fig. 2A and C) where classically only the face motor system is considered as being linked with language and speech networks (Hauk et al., 2004; Pulvermüller & Fadiga, 2010; Pulvermüller, 2005). This role of the PMv, and especially of the left PMv, in both speech and upper limb motor activity has already been investigated, often separately (van Geemen, Herbet, Moritz-Gasser, & Duffau, 2014; Vingerhoets, Nys, Honoré, Vandekerckhove, & Vandemaele, 2013). The preSMA is often consider as processing more cognitive aspect of motor control and language and is connected to cognitive regions compared to the SMAproper. It is interesting to note that the left PMv is widely connected to both preSMA supporting its cognitive role in movement and language beyond speech production or face motricity. Indeed, one can assume that DNMR site occurring in this region could be the consequence of more cognitive disruption than purely motor arrest as already proposed for the PMd in a recent study (Fornia et al., 2020).

DNMR did not show a somatotopic distribution over the preCG unlike what has been suggested by neuroimaging studies concerning language representation in the motor system (Boulenger et al., 2009; Esopenko, Borowsky, Cummine, & Sarty, 2008; Hauk et al., 2004). In fact, we assume that DNMR are widely distributed over the preCG in separate clusters as mentioned previously in part 2.2 for negative motor area. This hypothesis is confirmed by the difference in structural connectivity identified for each cluster leading us to presume that they have a different role.

The connectivity pattern of our clusters presents a dorso-ventral organization (Fig. 3). Dorsal cluster is mainly connected through the SLF I and II, and slightly with the AF whereas ventral cluster is widely connected through the SLF II, III, AF and the FAT. It is important to note that the lower part of the dorsal cluster is likely connected to the temporal lobe through the AF as classical connections of this fascicle do not project more dorsally over the rest of the cluster (Rojkova et al., 2016). This means that the AF takes probably only a little role in the network involving the dorsal cluster whereas it seems to have a major

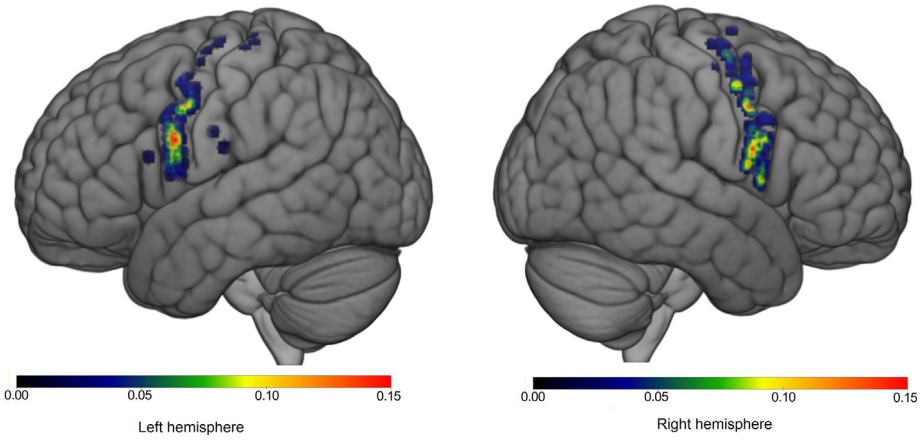

Fig. 1. Probabilistic map of dual negative motor responses. Color bar indicate the probability to elicit a DNMR on the corresponding hemisphere.

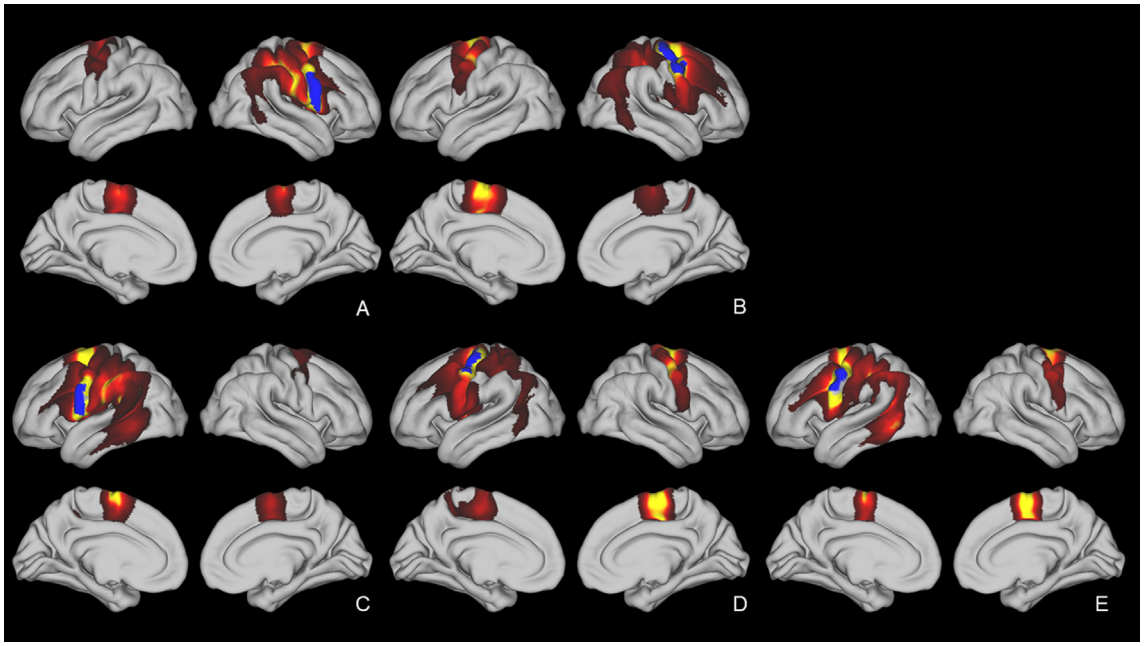

Fig. 2. Structural connectivity of each clusters. Clusters are shown in blue. Area connected to the cluster with a probability superior to 95% are shown in red-yellow gradient. Each figure (A–E) represents the ispi- and contralateral connections on the lateral and medial faces of the hemispheres. Data about clusters are coming from Rech et al. (2019). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

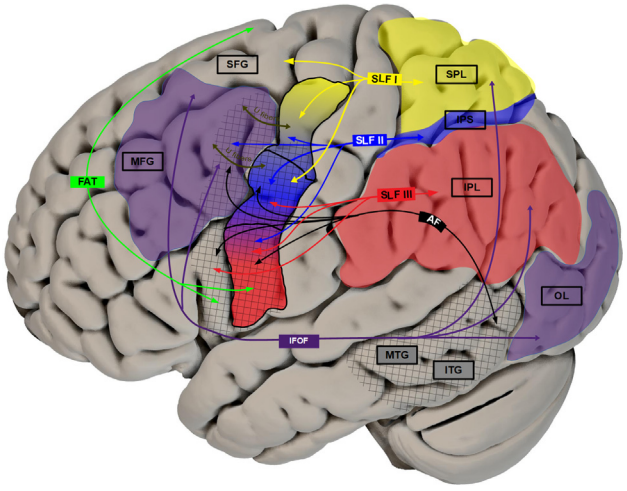

Fig. 3. Networks involving language and movement interactions. Clusters of DNMR are identified by black solid line over the preCG. Colors of the clusters correspond to the parietal origin of fibers. A gradient inside the preCG appears and is consecutive to a dorso-ventral progressive modification of the connectivity, from the SLF I (yellow), the SLF II (blue), and finally the SLF III (red). Cortical terminations of the AF are also shown with black crossed lines up to the lower part of the dorsal cluster. The cortical area identified thanks to the connectivity analysis are also known to be connected by several white matter pathways identified by DES. Parietal, occipital and temporal area are connected to the DLPFC thanks to the IFOF which is known to be crucial in semantic processes. Our results also showed that cortical termination of the IFOF are connected to our clusters thanks to U-fibers, linking then the semantic to the motor system. *SFG: superior frontal gyrus, MFG: middle frontal gyrus, SPL: superior parietal lobule, IPS: intraparietal sulcus, IPL: inferior parietal lobule, MTG: middle temporal gyrus, ITG: inferior temporal gyrus, OL: occipital lobe, SLF: superior longitudinal fasciculus, IFOF: inferior fronto-occipital fasciculus, AF: arcuate fasciculus, FAT: frontal aslant tract.* (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

role in the network of the left ventral cluster which is relevant given its implication in the phonological pathway. DNMR of the PMv confirmed the role of the SLF III in the articulatory loop as stimulation of this fascicle also induces speech arrest. Interestingly our results showed that SLFIII in both hemispheres might play a role in speech and motor processes. The third cluster on the left hemisphere presents a mixed pattern by sharing connections with the SLF I, II, III and the AF. Interestingly, connections through the AF to the temporal lobe are larger than those of the dorsal cluster but smaller than the ventral one. Consequently, there is a dorso-ventral continuum of the connections of our clusters to the temporal lobe. A continuum can also be found by considering the connections with the parietal lobe where projections evolve slightly dorso-ventrally from the superior parietal lobule to the inferior parietal one. In this case, this continuum is subserved by three components of the SLF (Rojkova et al., 2016). Interestingly, such segregation has been reported regarding the structural and functional connectivity within fronto-parietal networks. A spatial/motor dorsal component is involved in mental imagery, spatial working memory and voluntary oriented attention whereas a non-motor/spatial ventral component is mainly dedicated to mirror neurons, semantic and phonologic processing and verbal working memory (Parlatini et al., 2017). The intermediate component, as for our central cluster, shares fronto-parietal regions with the two others. It has been proposed that it might be involved in the adaptation of the tasks or in a modality independent conscious access (Dehaene & Changeux, 2011; Parlatini et al., 2017). This last hypothesis is very interesting as stimulation of this cluster elicits a DNMR but can also alter the motor awareness (Fornia et al., 2020). This would signify that DES might disturb interactions between language and action at a higher level than the output itself by interfering with networks involved in consciousness and/or attention, since it has been evidenced that DES can disrupt the inter-systems integration in a meta-networking account of brain processing (Herbet & Duffau, 2020).

The existence of DNMR over the preCG is in favor of an embodied cognition theory where concept would be grounded in sensorimotor system (De Stefani & De Marco, 2019; Gallese & Lakoff, 2005). This would explain several reports about the role of motor system in semantic processing, speech perception and comprehension (Dreyer &

Pulvermüller, 2018; Esopenko et al., 2008; Grisoni, Dreyer, & Pulvermüller, 2016; Pulvermüller & Fadiga, 2010; Schomers & Pulvermüller, 2016) and also why auditory language is able to interfere with grip force or gesture (Bernardis & Gentilucci, 2006; Pérez-Gay Juárez et al., 2019). However, the distribution of the DNMR as well as the structural connectivity of their clusters bring new insights into the cortical system of action and language. Indeed DNMR are located beyond the PMv, while in the classical view of this embodied theory temporal regions are connected to the PMv to form the action – perception circuit (Pulvermüller & Fadiga, 2010). This means that such model does not take account for larger distributed areas of the motor system able to process language and action. But assuming that dorsal premotor regions are involved in language (Boulenger et al., 2009; Dreyer & Pulvermüller, 2018; Marstaller & Burianová, 2015) requires to identify new areas in the circuit as the temporal structures are not directly connected to the PMd (Fig. 3). Therefore, the structural anatomy of the white matter pathways itself lets less likely the existence of a single "embodiment" network of language and action whose organization would be arranged somatopically (Hauk et al., 2004). Instead it seems likely that such embodiment occurs at the same time in a distributed way in several fronto-parietal and fronto-temporal networks working together and directed toward behavior instead of body parts such as the reaching and grasping network for example (Budisavljevic, Dell'Acqua, & Castiello, 2018). The ventral semantic stream, subserved by the IFOF, connects temporo-occipito-parietal areas to the DLPFC (Herbet, Moritz-Gasser, & Duffau, 2018; Wu, Sun, Wang, & Wang, 2016), itself connected to our clusters via U-fibers (Catani et al., 2012), linking then semantic and motor networks. Meanwhile, the dorsal phonological pathway subserved by the AF presents also strong and multiple connections with our clusters as well as the DLPFC (Sarubbo et al., 2016). Finally, Fig. 3 shows that articulatory and phonological loop, speech perception and production, semantic processes and motor system are strongly interconnected together at multiple level. The mirror system itself, considered as a plenty part of such action perception circuit, is known to be distributed on the parietal lobe beyond the ventral fronto-temporal circuit (De Stefani & De Marco, 2019; Rizzolatti & Sinigaglia, 2016). The dorso-ventral continuum reported as well as the fact that DNMR are not distributed in a somatotopic way does not refute the embodied theory but it rather makes it more complex as the motor system itself is not based on a somatotopic scheme (Catani, 2017; Graziano, 2016; Rech et al., 2019). This embodiment could finally not be as palpable as suggested by neuroimaging studies as it would be the consequence of complex interactions between networks in the framework of the meta-networking theory rather than being a point-to-point correspondence between language and motor system (Herbet & Duffau, 2020). Consequently, computational models of action perception circuits require to integrate parietal and premotor areas connected by dorsal and ventral pathways as well as cortico-sub-cortical connections with basal ganglia through the FST and interhemispheric balance in order to fit the findings gained from electrophysiological studies (Garagnani, Wennekers, & Pulvermüller, 2008).

3.5. Limits

Despite the language assessment only involved a naming task, DNMR were identified whole over the preCG, including sites classically dedicated to speech perception in the action perception circuit such as the PMv (Pulvermüller & Fadiga, 2010). Then, DES of the PMv could have elicit more cognitive effect than purely motor one, perhaps by interfering with the mirror mechanism (Rizzolatti & Sinigaglia, 2016).

Distribution of DNMR spares the most dorsal part of the preCG, just caudally to the SFG in both hemispheres. This might be explained by the fact that interaction between movement and language could involve more the hand than the rest of the body because synchronization between gesture and speech is often a matter of hand and arm movement (Bernardis & Gentilucci, 2006).

It was not possible to identify homotopic fibers linking both PMv. This might be due to technical limit, but it is noteworthy that heterotopic fibers connecting PMd and PMv could be revealed. The potential lack of connection between both PMv could also explain the lack of plasticity of the left PMv (van Geemen et al., 2014).

Finally, few structures outside the precentral gyrus are responsible of DNMR. The postcentral gyrus was involved, at the level of the face and the hand somesthetic area, likely by their U-shape connections to the primary and premotor cortex. The pars opercularis was responsible of one single response, and a DNMR, among the 117 patients. We could not rule out the possibility that spatial distribution of DNMR over the preCG and postCG could be modified by the presence of the tumor: however, these areas were only invaded in 5% and 6% of cases, respectively. The SFG, MFG and IFG were invaded in 22%, 18% and 9% of cases, respectively. Nevertheless it seems unlikely that the tumor modified deeply the spatial distribution of the DNMR at this level, especially because there were elicited only one time over the IFG and never over the SFG and MFG, even in the 91%, 78% and 82% of cases in which these structures were not invaded. This does not mean that such areas are not involved in both speech and motricity but likely that they act at a different level of integration.

4. Conclusion

Evidences gained from literature about DES confirmed that language and motor systems share common neural structures at cortical and subcortical levels where interactions between both functions occur to select, synchronize adapt and/or mentalize behavior. Our experimental study confirmed these findings and shed the light on multiple areas of specific interactions between speech and upper limb motricity at the level of the precentral gyrus whose organization is far from the somatotopy previously suggested. The structural connectivity of such areas revealed that networks involved in speech and upper limb motricity are parallel and bilaterally distributed on the parietal, temporal and frontal lobes. They shared interconnections with hubs connected with semantic, phonologic, articulatory and motor pathways providing an embodiment of language at the level of *meta*-network rather than a point-to-point correspondence between temporal and precentral areas.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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