

Structural and Functional Integration Between Dorsal and Ventral Language Streams as Revealed by Blunt Dissection and Direct Electrical Stimulation

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Abstract: The most accepted framework of language processing includes a dorsal phonological and a ventral semantic pathway, connecting a wide network of distributed cortical hubs. However, the cortico-subcortical connectivity and the reciprocal anatomical relationships of this dual-stream system are not completely clarified. We performed an original blunt microdissection of 10 hemispheres with the exposition of locoregional short fibers and six long-range fascicles involved in language elaboration. Special attention was addressed to the analysis of termination sites and anatomical relationships between long- and short-range fascicles. We correlated these anatomical findings with a topographical analysis of 93 functional responses located at the terminal sites of the language bundles, collected by direct electrical stimulation in 108 right-handers. The locations of phonological and semantic paraphasias, verbal apraxia, speech arrest, pure anomia, and alexia were statistically analyzed, and the respective barycenters were computed in the MNI space. We found that terminations of main language bundles and functional responses have a wider distribution in respect to the classical definition of lan-

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Received for publication 20 March 2016; Revised 7 May 2016; Accepted 24 May 2016.

DOI: 10.1002/hbm.23281

Published online 3 June 2016 in Wiley Online Library (wileyonlinelibrary.com).

guage territories. Our analysis showed that dorsal and ventral streams have a similar anatomical layer organization. These pathways are parallel and relatively segregated over their subcortical course while their terminal fibers are strictly overlapped at the cortical level. Finally, the anatomical features of the U-fibers suggested a role of locoregional integration between the phonological, semantic, and executive subnetworks of language, in particular within the inferoventral frontal lobe and the temporoparietal junction, which revealed to be the main criss-cross regions between the dorsal and ventral pathways. *Hum Brain Mapp* 37:3858–3872, 2016. © 2016 Wiley Periodicals, Inc.

Key words: language network; white matter; brain connectivity; blunt dissection; subcortical mapping; direct electrical stimulation

INTRODUCTION

Evolution and progress are based on the human ability to communicate. The organization of language network has been one of the most studied fields over the last two centuries. The first embryonic “network theory” regarding the anatomico-functional basis of language processing was proposed by Carl Wernicke in 1874 [Wernicke, 1874a,b]. Starting from anatomico-clinical observations provided by Paul Broca [Broca, 1861] about the role of the posterior inferior frontal gyrus (the so-called Broca’s area [IFG]), Wernicke argued that there existed a large functional network. This network included the posterior temporal lobe (still known as Wernicke’s territory), as a hub subserving the semantic motor and the language sensitive content, and the Broca’s area, as the center of motor elaboration of language production [Wernicke, 1874a,b]. In 1965, this associationist model was renewed and strongly improved by Norman Geschwind, who proposed a wider, parallel, and integrated network, involving also the inferior parietal lobule (IPL), a region which is still known as Geschwind’s territories [Catani and Ffytche, 2005 ; Geschwind 1965a,b].

Recent advancements in neuroimaging, and direct electrical stimulation (DES) confirmed the role of these regions in language elaboration and demonstrated the crucial participation of other neighboring cortices [Benzagmout et al., 2007; Duffau et al., 2008, 2014; Tate et al., 2014]. According to this model [Duffau, 2008; Hickok and Poeppel, 2007; Price 2012; Vigneau et al., 2006], Broca’s area, including the pars opercularis (POp), the pars triangularis (PTri), and the pars orbitalis (POrb), is involved in different functional aspects. In particular, articulation and phonology prevail in the posterior portion, while syntactic and semantic processing involve the anterior part [Koelsch et al., 2002; Uddén and Bahlmann, 2012]. Recent studies have showed that this specialized frontal area extends within the ventral pre-motor cortex (VPMC) and the dorsolateral pre-frontal cortex, especially for articulatory and semantic elaboration, respectively [Duffau et al., 2005; Sarubbo et al., 2015a,b; Tate et al., 2014]. The classical Wernicke’s territory (i.e., the posterior third of the superior temporal gyrus [STG]), and the posterior and middle portion of the middle temporal gyrus (MTG) were proposed as cortical substrates for the access to semantic

information in the form of a sound-meaning interface [Hickok, 2009]. In addition to the classical high-specialized language areas around the posterior third of the superior temporal sulcus (STS), and the posterior planum temporale (i.e., Heschl’s gyrus), the involvement of other temporal territories in the language network was hypothesized, namely: (i) the middle portions of the left MTG for word comprehension [Turken and Dronkers, 2011]; (ii) the anterior temporal cortex for basic combination and/or integration of semantic representations with context [Lau et al., 2008]; (iii) the left posterior inferior temporal cortex for phonological and semantic modulation during reading of pseudowords and irregular words [Zemmoura et al., 2015]; (iv) and the left anterior temporal lobe for setting semantic representations [Lambon Ralph et al., 2009]. Finally, the IPL was confirmed as a sensori-motor interface area for language elaboration [Hickok and Poeppel, 2007], which may play a role in verbal working memory and language performance [Buchsbaum et al., 2011a,b; Meyer et al., 2012].

Definitely, serial and parallel elaborations occur continuously across all of these cortices, which are linked together by redundant circuits of input/output fibers [David et al., 2011; Friederici, 2011; Sarubbo et al., 2015a,b], segregated in parallel networks, subserving multiple aspects of elaboration, and terminating in different ultra-specialized cortices within both hemispheres, according to a “connectomic” view of brain organization [Sporns et al., 2005; Sporns 2013a,b]. In this context, the white matter (WM) constitutes the structural substrate for the functional integration between these territories. Already at the end of the 19th century, the unique data provided by the anatomists of the first “fibers era” [Déjerine and Dejerine-Klumpke, 1895, 1901; Klingler, 1935; Meynert, 1868] led the pioneers of language theory to realize the essential role of connectivity, and to demonstrate that injury to long fibers causes clinical deficits [as the arcuate fascicle (AF) in conduction aphasia model] [Wernicke, 1874a,b].

Nowadays, diffusion imaging tractography has led the neuroscientific research into a new “fibers era,” providing fascinating data about the anatomy of the human WM [Catani and Thiebaut de Schotten 2008, 2013]. However, as a consequence of the technical limitations of tractography, the interest for blunt microdissections has been renewed and the relevant techniques have been improved,

providing unique evidences about structure and connections of long and short WM fibers [Catani et al., 2012; De Benedictis et al., 2014; Fernández-Miranda et al., 2015; Martino et al., 2011; Sarubbo et al., 2013]. Moreover, there are no neuroimaging or anatomical techniques providing specific information about the functional role of WM tracts. Conversely, studies based on DES, lesions (i.e., stroke), or pathological models are contributing to improve our knowledge about the role of specific pathways in the different aspects of language processing [Duffau, 2015; Fang et al., 2015; Rolheiser et al., 2011; Sarubbo et al., 2015a,b].

Currently, a dual stream model, based on a dorsal and ventral pathway, is widely accepted [Axe et al., 2013; Dick et al., 2014; Duffau et al., 2014; Griffiths et al., 2013]. The dorsal stream, including long WM tracts running around the Sylvian fissure and connecting the frontal to the temporal and parietal lobes, is deputed to the integration of sensory percepts and internal models [Weiller et al., 2011; Yagmurlu et al., 2015]. The dorsal stream is composed of the AF, and the indirect anterior and indirect posterior components of superior longitudinal fascicle (SLF). The ventral stream connects the frontal cortices to the occipital, parietal and temporal lobes, via the external capsule (EC). This pathway relates to different aspects of semantic elaboration [Saur et al. 2008], and the main core is composed of the inferior fronto-occipital fascicle (IFOF), the inferior longitudinal fascicle (ILF), and the uncinate fascicle (UF) [Moritz-Gasser et al., 2013]. These bundles together constitute the most accepted long-connectivity core for language elaboration.

However, the exact anatomo-functional subcortical setting of the language network has not been clearly defined so far, especially concerning the termination territories of the fascicles composing the dorsal and ventral streams, some structural features of the different tracts, and their reciprocal relationships along their course and/or at the termination sites. An accurate knowledge of the topographical distribution of the main functional hubs of terminal fibers could improve our vision of the “language connectome.”

This study proposes, for the first time to our knowledge, detailed anatomo-functional evidences obtained by: the sequential and contemporary microdissection of the main bundles and cortical regions of terminations involved in language elaboration; the integration and discussion of the functional evidences provided by axonal DES, with special interest on the topographical distribution of the different functional clusters in close proximity to the cortical territories of termination. The aim of our work was to provide an integrated structural and functional overview of the different modalities of language elaboration, based on the minimal anatomical WM connectivity at short and long range.

MATERIALS AND METHODS

Dissection

We selected 10 cerebral hemispheres (five left and five right) which were previously extracted and fixed in a 10%

formalin solution for 40 days and then frozen for 30 days at -80°C . After gradual defrosting of the specimens, we gently removed the arachnoids and vessels. An accurate analysis of the cortical surfaces excluded major anatomical variability of the sulco-gyral anatomy. Using wooden spatulas, we started a micro-dissection ($\times 5$) by removing the gray matter of the cerebral sulci and preserving the gray matter at the top of the gyri, to obtain the correct definition of the termination territories of the main bundles explored.

The dissection was continued sequentially in a lateromedial direction, to expose the U-shaped locoregional fibers, two components of the SLF (anterior and posterior indirect components [SLF]), the arcuate fasciculus (AF), the IFOF, the ILF, and the UF. To improve the anatomical definition of the deeper layers of WM, the specimens underwent progressive formalin re-injection and frost-defrost process, according to the method previously described by our group [De Benedictis et al., 2012, 2014; Sarubbo et al., 2015a]. The integrity of each fascicle was carefully preserved to define their entire course.

We focused our analysis on the relationships between the explored association bundles (indirect posterior and anterior indirect portions SLF, AF, IFOF, and ILF). To provide an integrated view of the reciprocal anatomical locations of these pathways, we preserved their main stems (i.e., the region of highest-density and concentration of fibers). We progressively collected the termination territories, and we stored high-resolution pictures of the specimens. In the Results section, unless differently specified, we reported exclusively the termination territories systematically observed in all the specimens.

Analysis of Distribution of the DES Data

One-hundred eight patients were submitted to cortico-subcortical mapping during awake surgery, as described in a previous study [Duffau et al., 2005, 2014; Sarubbo et al., 2015b]. We analyzed the location of 93 subcortical functional responses (24 phonological paraphasias; 19 semantic paraphasias; 22 verbal apraxia; 14 speech arrest; 10 pure anomia; 4 alexia) related to language elaboration. The spontaneous language production was monitored with counting test (series from 0 to 10) and repetition test [Fernández Coello et al., 2013]. The phonological and semantic aspects of language processing (i.e., semantic and phonological paraphasias; pure anomia) and reading (i.e., alexia or reading disturbances) were assessed, respectively, with the naming [denomination object 80 (DO 80)] and reading test, as previously reported [Duffau et al., 2003, 2005; Duffau, 2008; Fernández Coello et al., 2013; Goodglass and Kaplan, 1971; Metz-Lutz et al., 1991; Sarubbo et al., 2015].

The functional points, identified during intraoperative DES and stored by numerical tags in detailed high-resolution pictures, were included as circular ROIs (with Osirix, <http://www.osirix-viewer.com>) in the axial volumetric T1 by the first author (S.S.), comparing the

anatomical landmarks (boundaries of the surgical cavities, sulco-gyral anatomy, vascular structures, etc.) of the single picture with the axial volumetric T1 (3-months post-operative) and the sagittal and coronal sequences oriented according to the position of the head during the surgery, as previously described [Sarubbo et al., 2015b]. We considered exclusively the responses sited at the border of the surgical cavities, within 2 cm from the cortex and included in the WM extension of the cortical ROIs according to the JHU Atlas (as an instance SMWM_R = SUPRAMARGINAL WM right). In this way, we focused the analysis on the cortico-subcortical functional responses located within the main termination territories (i.e., frontal, temporal, parietal, and occipital lobes) of the bundles included in the dissection study (i.e., indirect anterior and posterior portion of SLF, AF, IFOF, ILF, UF). According to the methods previously described by our group [Sarubbo et al., 2015b], the volumetric T1 sequences were spatially registered to the MNI space (1 mm³ voxel spatial resolution) and the resulting registration models were used for the co-registration of the ROIs of the functional responses, using FSL (<http://www.fmrib.ox.ac.uk/fsl>). Finally, the anatomical location of the functional responses and of the clusters resulting from the topographical analysis (see chapter below) was related to the results of post-mortem dissections using 3D reconstruction of the MNI 152 brain (1 mm³ voxel spatial resolution) and the cortical ROIs of the JHU Atlas.

Cluster Analysis

We analyzed the clusters using the statistical program R (version 3.1.2; <http://www.r-project.org/>). We computed the barycenter position of the 93 functional responses in the MNI space [Sarubbo et al., 2015a,b]. For each class of functional responses, we determined whether they should be represented as single or multiple clusters. The classes of functional responses with a significance level of 0.05 of the Duda–Hart statistic (*dudahart2* R function) [Duda and Hart, 1973] underwent cluster analysis; other classes of functional responses were presented as single cluster.

As regards the classes of functional responses with significance level of 0.05 of the Duda–Hart statistic, we used two different clustering algorithms, namely partition-around-medoids (*pam* R function) [Reynolds et al., 1992], a more robust version of K-means, and agglomerative hierarchical clustering (*agnes* R function) [Kaufman and Rousseeuw, 1990]. Both algorithms were applied by varying the number of clusters from 2 to 20. For each method, we selected the optimal number of clusters by computing the silhouette information (*silhouette* R function) [Rousseeuw, 1987]. We considered the algorithm relevant to the smallest number of optimal clusters. For each cluster provided by the selected clustering algorithm, we computed the mean and standard deviations along the three main directions in the MNI space.

RESULTS

U-Fibers Analysis of Language Territories

We considered as U-fibers exclusively the short fibers connecting adjacent gyri or their portions. The anatomical analysis (focused on the frontal lobe, the temporal lobe and the IPL) showed two main orientations: horizontal and vertical, depending on the orientation of the respective gyri. The U-fibers connecting horizontal parallel gyri have a vertical orientation, while the U-fibers linking vertical parallel gyri have a horizontal course. We found a high concentration of horizontal U-fibers within the IFG, compared to the other parts of the frontal lobe, providing a high intra-gyral structural connectivity. This result is the consequence of the high number of short intra-gyral sulci, which separate the parallel vertical organization of frontal opercula (VPMC, POp, PTri, POB), in respect to the MFG and the SFG (Fig. 1a).

Similar findings were evident within the IPL. In fact, microdissections showed a prevalent horizontal U-fibers orientation between SMG and AG due to the vertical sulcal organization of this region, including the supramarginal sulcus and the first, second, and third caudal branches of the STS (respectively, cSTS1, cSTS2, cSTS3) [Zlatkina and Petrides, 2014]. Particularly, the horizontal U-fibers underlying the cSTS1, which constitute a real elongation of the STS within the IPL, provide a unique and direct connection between the SMG/AG and the posterior thirds of STG and MTG (Fig. 1b). This continuous layer of U-fibers is characterized by a progressive torsion from the horizontal to the vertical orientation, which is typical of the U-fibers of the temporal lobe. Within the temporal lobe, in fact, the U-fibers have a mostly vertical orientation, and connect the parallel and horizontally facing STG, MTG, and ITG, all over the course of the STS and inferior temporal sulcus (ITS) (Fig. 1a).

Long Association Fibers

In all the specimens, we found fibers and the respective stems of the AF, the indirect posterior and anterior components of the SLF, the IFOF, the ILF, and the UF. We did not observe significant variations between the specimens regarding the stem location and the reciprocal anatomical relationships.

We identified the stem of the anterior indirect portion of the SLF (Fig. 2a) below the U-fibers connecting the most ventral cortices of the pre- and post-central gyri (PreCG and PostCG, respectively). We detected the main anterior terminations of this bundle within the VPMC, the ventral and dorsal Pop, and the ventral portion of the posterior third of the MFG. Posterior terminations of this SLF branch were prevalently located in the anterodorsal portion of the SMG and the AG, and in the posterior part of the STG. In all the specimens, we detected the stem of the indirect posterior component of the SLF (Fig. 2b) below

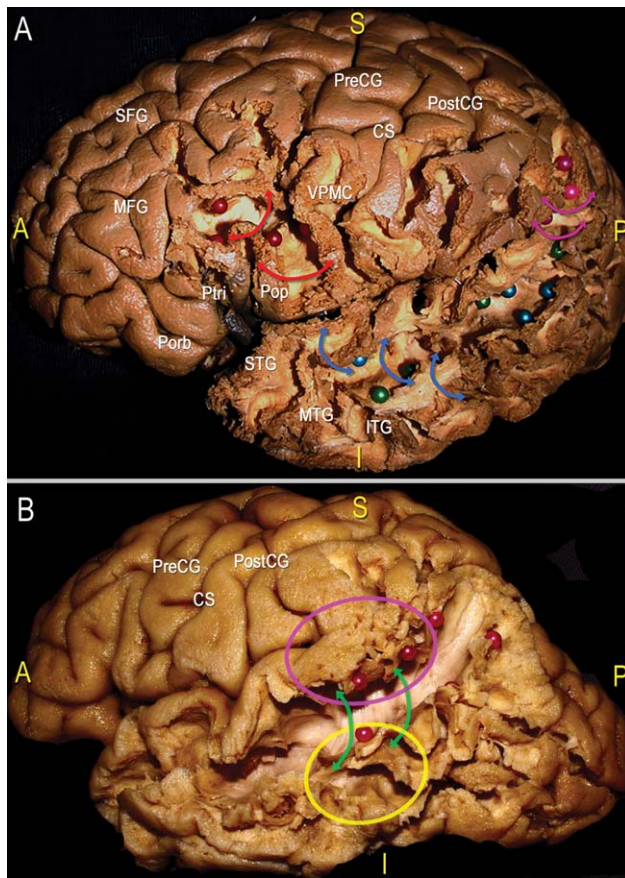


Figure 1.

In picture A, we highlighted: (1) a detail of the U-fibers within the posteroventral frontal lobe, showing the prevalent horizontal short connections in the classical Broca's area (red arrows, highlighting the connections between the ventral and dorsal POp, PTri, and VPMC); (2) the continuous vertical short connections between the STG, the MTG, and the ITG in the depth of the STS and the ITS (blue arrows); (3) the horizontal fibers between the SMG and the AG and the SMG (pink arrows). In picture B, we depicted the typical homogenous and continuous layer of horizontal U-fibers (green arrows). These short fibers directly connect the IPL (violet circle) with the posterior two-third of the STG and the MTG (yellow circle) (i.e., the classical definition of Geschwind and Wernicke territories, respectively) and are characterized by a progressive torsion from the horizontal to the vertical orientation typical of the U-fibers connecting the temporal gyri. *Abbreviations:* AG: angular gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; ITS: inferior temporal sulcus; MTG: middle temporal gyrus; POp: pars opercularis; PTri: pars triangularis; SMG: supramarginal gyrus; STG: superior temporal gyrus; STS: superior temporal sulcus; VPMC: ventral pre-motor cortex.

the posterior third of the STG, at the border with the occipital lobe. Ventral terminations of this bundle resulted mostly restricted to the posterior and middle thirds of the

MTG and the STG. We observed ventral terminal fibers also in the most anterior portion of the MOG (6/10, 4 left and 2 right). The dorsal terminations were prevalent in the posteroventral portion of the SMG and the AG within the IPL. We systematically detected the stem of the AF (Fig. 3) behind the posterosuperior border of the circular sulcus of the insula, just below the temporoparietal junction. Anterior terminations of the AF were regularly reported in the anterior portion of the VPMC, in the POp (particularly, dorsal POp), and in the ventral portion of the posterior MFG. Posterior terminations were found in all the specimens within the posterior and middle thirds of the MTG, the STG and in the middle third of the ITG.

We identified the stem of the IFOF (Fig. 4a) at the level of the most ventral portion of the EC in all the specimens. The IFOF was separated from the UF stem, by excluding all the fibers directed to the temporal pole. Following the posterior course of this tract, we found terminations within the temporobasal region (fusiform and basal posterior portion of the ITG) in six specimens (4 left and 2 right), within the most lateral cortices of the pre-cuneus in eight specimens (5 left and 3 right), and within the lingula, the occipital pole, the SOG, the MOG, and the IOG in all the specimens (Fig. 4c). The superficial layer of the stem fibers presents with a constant and homogeneous distribution within the ventral portion of PTri and PORb of the IFG. Following the deeper fibers of the fan-shaped stem within the frontal lobe, we found a posterior and more vertical portion of the IFOF directed to the middle and posterior thirds of the MFG and the SFG, crossing the horizontal course of the anterior portion of the AF and the indirect anterior component of the SLF (Fig. 4b).

In all the specimens, we detected the stem of the ILF within the lateral WM at the temporo-parieto-occipital junction. These fibers have a constant antero-inferior course from the dorsolateral occipital cortex of the SOG and the MOG (dorsal component), the lingula and the fusiform gyrus (FG) (ventral component) to the middle and anterior thirds of the lateral and inferior portion of the MTG, the lateral and basal portion of the ITG, and the anterior and middle temporobasal cortices (Fig. 4d).

In all the cases, we dissected the stem of the UF (Fig. 5a) in the most anterior and ventral portion of the EC, just anterior and dorsal to the IFOF. The UF fibers have a typical arch-shaped course around this portion of the EC and connect the anterior third of the MTG and the STG and the temporal pole with the frontal lobe. Particularly, we found two main layers of fibers. The superficial layer partially covers the adjacent IFOF stem and connects the anterior third of the STG and the MTG with, respectively, the IFG (namely ventral portions of PTri and PORb), the ventral orbitolateral cortex and the middle third of the MFG. Interestingly, we observed further connections attributable to this superficial component of the UF, reaching the posterior and middle thirds of the SFG and MFG, respectively (Fig. 5b). The deeper layer runs anterior and ventral to the

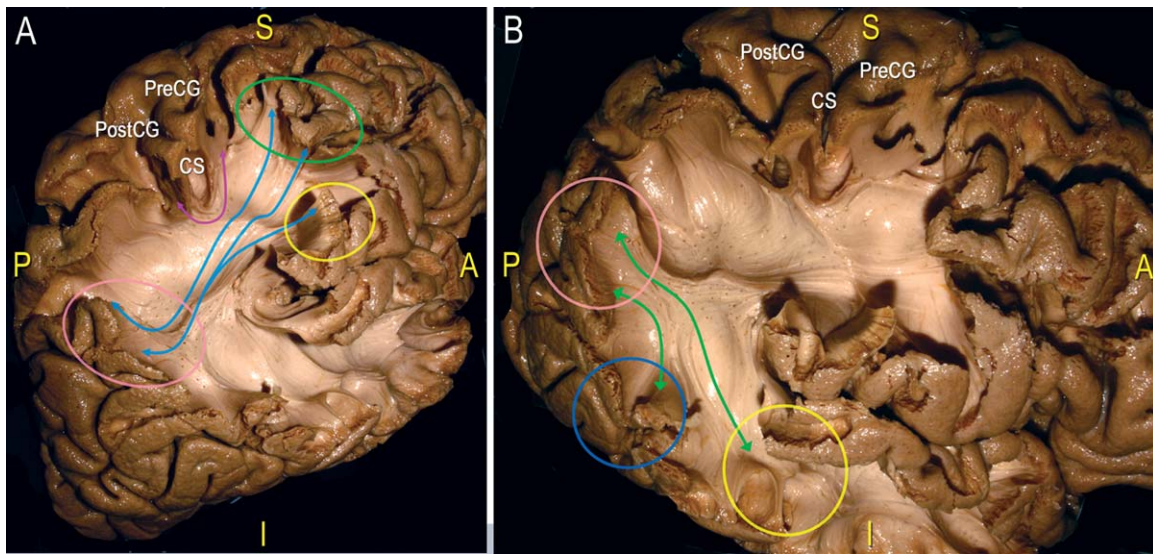


Figure 2.

In picture A, the stem of the indirect anterior SLF is showed below the CS (violet arrow) with the main anterior terminations in the VPMC, the ventral and dorsal POp (yellow circle), the ventral portion of the posterior third of the MFG (green circle) and the main posterior terminations in the anterodorsal portion of the SMG, and in the AG (pink circle). In picture B, the stem of indirect posterior component of the SLF is showed below the posterior third of the STG at the occipitotemporal junction. Ventral terminations were found in the posterior and middle

thirds of the MTG and the STG and in the anterior portion of the MOG (yellow and blue circles). Dorsal terminations are prevalent in the posteroventral portion of SMG and AG (pink circle). *Abbreviations:* AG: angular gyrus; CS: central sulcus; MFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; POp: pars opercularis; SLF: superior longitudinal fascicle; SMG: supramarginal gyrus; STG: superior temporal gyrus; VPMC: ventral pre-motor cortex. [Color figure can be viewed at wileyonlinelibrary.com]

IFOF stem and it connects the temporal pole with the frontal orbitolateral and orbitobasal cortices (including the gyrus rectus), and the frontal pole (Fig. 5b).

Reciprocal Anatomical Analysis: Course and Terminations Sites

The course of the indirect anterior SLF is parallel and lateral to the anterior branch of the AF. These fibers are paired and adjacent, from the posteroventral cortices of the frontal lobe up to the stem of the AF. Within the frontal region, we observed a high degree of overlapping between terminations of the AF, which are more anterior and dorsal, and the indirect anterior SLF. Moreover, we found a strict relationship between the terminal SLF/AF fibers, running with a superficial and posterior-to-anterior horizontal course, and the vertical fibers of the IFOF. In fact, terminations of the superficial component of the IFOF (i.e., PTri and POrb) are more anterior and ventral in respect to the SLF/AF (i.e., VPMC and POp). Conversely, the horizontal terminal fibers of the SLF/AF and the vertical deeper fibers of the IFOF cross at the level of the middle and posterior thirds of the IFG and the IFS (Fig. 4b). The terminations of the deep components of the IFOF are

more dorsal and anterior (i.e., posterior and middle third of the MFG) in respect to the SLF/AF (i.e., ventral portion of posterior third of the MFG).

At the temporoparietal junction, the indirect posterior SLF is parallel to the descending branch of the AF, but terminations of the AF are generally more inferior and more anterior. In the cortices of the SMG and AG (i.e., IPL), the terminations of the indirect anterior SLF are adjacent (anterodorsal located) to the terminations of indirect posterior SLF (posteroventrally located). At this level, the AF follows a C-shaped course around the posterior profile of the insula and crosses the IFOF fibers running on a medial layer with a horizontal orientation (Fig. 4a). The posterior portion of the ILF runs laterally to the inferior portion of the IFOF and to the inferior optic radiation (OR) with a mild inferior orientation directed to the inferior and temporal basal cortices (Fig. 4d).

Direct Electrical Stimulation

The analysis of DES data (Fig. 6) within the frontal lobe showed: (i) two separated cortico-subcortical clusters for semantic disturbances (i.e., disorders of the meaning of the word), respectively, located within the most ventral

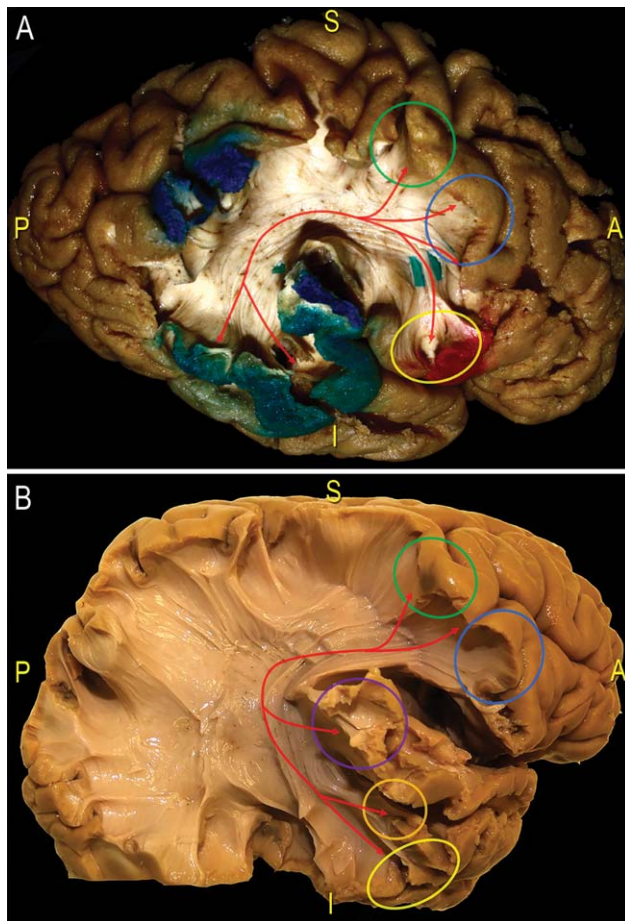


Figure 3.

In picture A, the full course of the more dorsal portion of the AF (namely, the deeper branch of the dorsal stream) is showed with the frontal terminations (yellow circle) in the VPMC and POp (classical Broca's area, red cortex) and in the posterior third of the MFG (green and blue arrow), and the temporal terminations in the posterior and middle thirds of the MTG and the STG and in the middle third of the ITG (green cortex). In picture B, a segmentation of the most ventral portion of the AF over its full course showing the terminal territories in temporal [STG (red circle), MTG (orange circle) and ITG (yellow circle)] and frontal lobes [VPMC and POp (blue circle), posterior third of the MFG (green circle)]. *Abbreviations:* AF: arcuate fascicle; ITG: inferior temporal gyrus; MFG: middle frontal gyrus; MTG: middle temporal gyrus; POp: pars opercularis; STG: superior temporal gyrus; VPMC: ventral pre-motor cortex. [Color figure can be viewed at wileyonlinelibrary.com]

portion (cluster_1_semantic: $x = -30.1$, $y = 27.9$, $z = 5.6$) of the middle third of IFG (i.e., PTri), and within the posterior third of the MFG at the border with the Pre-CG (cluster_2_semantic: $x = -26.4$, $y = 13.6$, $z = 43.0$); (ii) two separated clusters for speech arrest (i.e., interruption of counting test without involuntary muscle contraction)

within the most ventral portion of the POp at the border with the VPMC (cluster_1_speecharrest: $x = -43.0$, $y = 17.0$, $z = 12.5$) and at the border between the posterior third of the MFG and the mid-dorsal portion of the Pre-CG (cluster_2_speecharrest: $x = -37.4$, $y = 2.4$, $z = 36.7$), respectively; (iii) one subcortical cluster for phonological paraphasias (i.e., disorder of the phonological form of the word) at the border between the dorsal POp and PTri and the ventral and posterior portion of the adjacent MFG (i.e., posterior third of the IFG [cluster_1_phonological: $x = -36.0$, $y = 16.2$, $z = 21.6$]); (iv) one subcortical functional cluster for verbal apraxia (i.e., disorder of language planning and articulation) at the border between the dorsal portion of the POp and the ventral posterior third of the MFG (cluster_1_verbalapraxia: $x = -39.1$, $y = 10.5$, $z = 24.0$).

The analysis of DES data within the posterior temporal area showed: (i) one subcortical cluster for phonological paraphasias (cluster_2_phonological: $x = -50.4$, $y = -37.5$, $z = -9.8$) within the middle third of the MTG at the border with the ITG; (ii) one subcortical functional cluster for semantic disturbances within the WM of the posterior third of the ITG at the border with the adjacent MTG (i.e., posterior third of the ITS [cluster_3_semantic: $x = -42.5$, $y = -52.3$, $z = -1.6$]); (iii) one subcortical cluster for pure anomia (i.e., not related to motor, praxic, and visual disturbances nor associated to semantic or phonological deficits) within the posterior third of the MTG at the border with the STS (cluster_1_amodalnomia: $x = -58.0$, $y = -31.9$, $z = -0.1$); (iv) one subcortical cluster for reading disturbances (i.e., alexia) within the posterior third of the ITG (cluster_1_alexia: $x = -47.0$, $y = -54.0$, $z = -11.8$).

The analysis of DES data within the IPL showed: (i) one subcortical cluster for pure anomia (cluster_2_amodalnomia: $x = -42.6$, $y = -49.5$, $z = 34.4$) within the WM of the posterior and dorsal portion of the AG; (ii) one subcortical cluster for verbal apraxia in the anteroventral portion of the SMG (cluster_2_verbalapraxia: $x = -46.8$, $y = -35.2$, $z = 32.7$).

DISCUSSION

In this work, we analyzed the structural connectivity of the language network, in the light of the most accepted framework regarding the anatomo-functional organization of linguistic processing, which describes a dorsal and a ventral stream connecting the frontal, temporal, parietal, and occipital lobes [Axe et al., 2013; Dick et al., 2014; Griffiths et al., 2013; Hickok and Poeppel 2007; Saur et al., 2008]. To clarify the short- and long-range connectivity of this network, we performed blunt micro-dissections, and we sequentially exposed the course and terminations of six association pathways (i.e., indirect anterior and posterior portions of SLF, AF, IFOF, ILF, and UF) and the respective locoregional U-fibers anatomy. Then, we matched the anatomical data with the results coming from axonal DES of terminal fibers. Currently, axonal DES

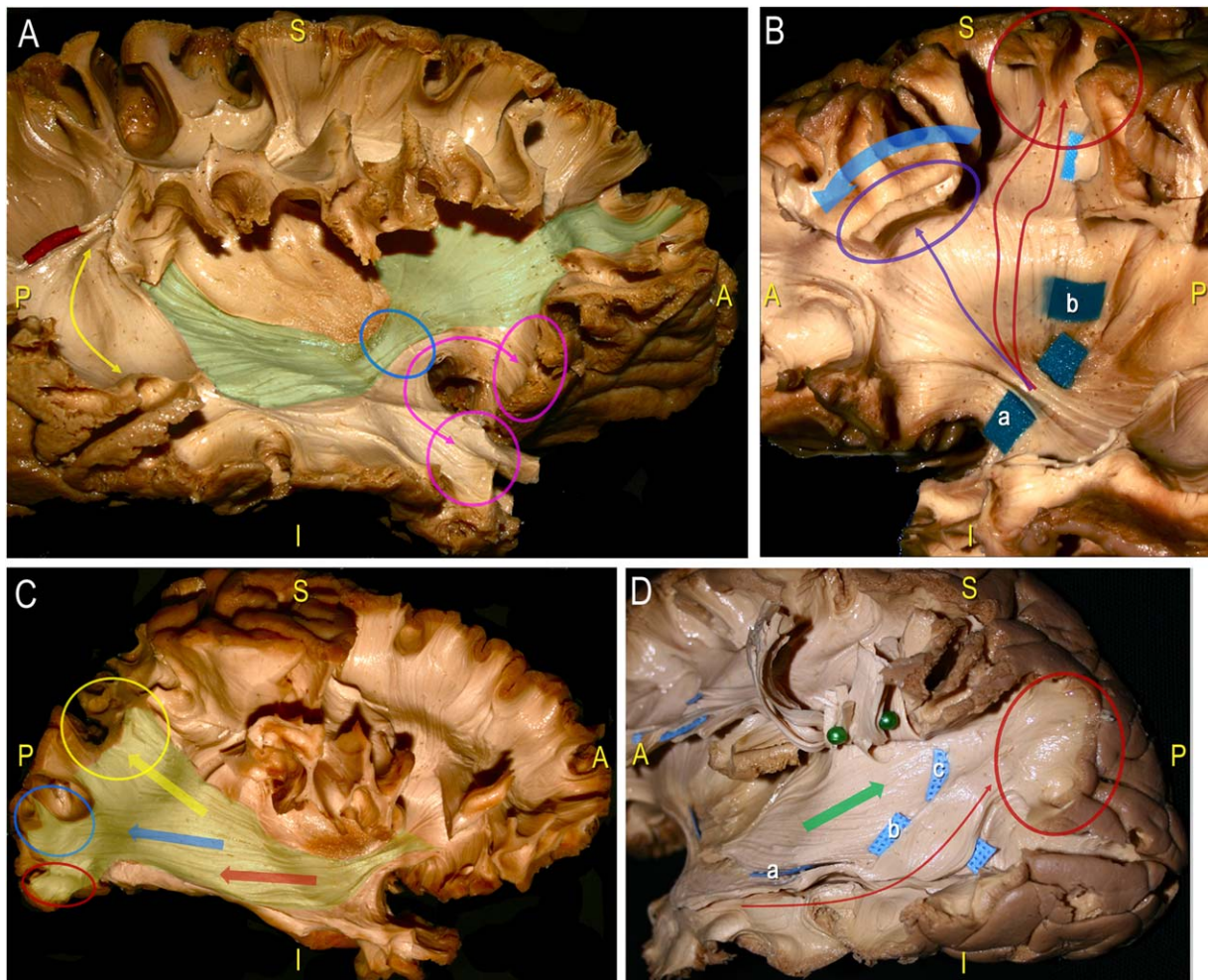


Figure 4.

In picture A, we described the relationship between the IFOF stem (green fibers) and the superficial layer of the UF (pink arrows) in the anteroventral third of the EC (blue circle). We exposed the fibers cross between the IFOF and the descending portion of the AF, below the posterior half of the temporal lobe. In picture B, a detail of the superficial and deep terminations of IFOF in the PTri (blue arrows) and posterior third of MFG and SFG (red arrows), coming from the fun shaped stem (highlighted by a blue tag) in the EC. In picture C, we exposed the posterior terminations of IFOF (green fibers) in the precuneus and dorsolateral occipital cortex (yellow circle), the lingual, temporal basal cortices, and the FG (blue and red circle).

Picture D depicts a detail of the layers of fiber dissection at the temporo-parieto-occipital junction with the demonstration of the ILF connecting the dorsolateral occipital cortex (SOG and MOG) with the ventrolateral portion of the middle third of the MTG and the lateral and basal middle third of the ITG. *Abbreviations:* EC: external capsule; FG: fusiform gyrus; IFOF: inferior fronto-occipital fascicle; ILF: inferior longitudinal fascicle; ITG: inferior temporal gyrus; MFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; PTri: pars triangularis; SFG: superior frontal gyrus; SOG: superior occipital gyrus; UF: uncinata fascicle. [Color figure can be viewed at wileyonlinelibrary.com]

provides the unique opportunity of investigating the functional properties of WM fibers [Duffau et al., 2008; Duffau, 2014; Sarubbo et al., 2015a,b]. We investigated the topographical distribution, the reciprocal relationships and the functional implications of WM pathways involved in the different aspects of language elaboration (semantic, phonological, articulatory, verbal planning, reading), including

in the analysis of the association bundles with the most widely accepted role of the dual-stream language network in the core of long-range connectivity, and collecting exclusively the functional subcortical responses in close proximity to the terminal fibers. It is worth noting that a possible involvement of other tracts (as the frontal aslant tract and the middle longitudinal fascicle MdIF) is currently under

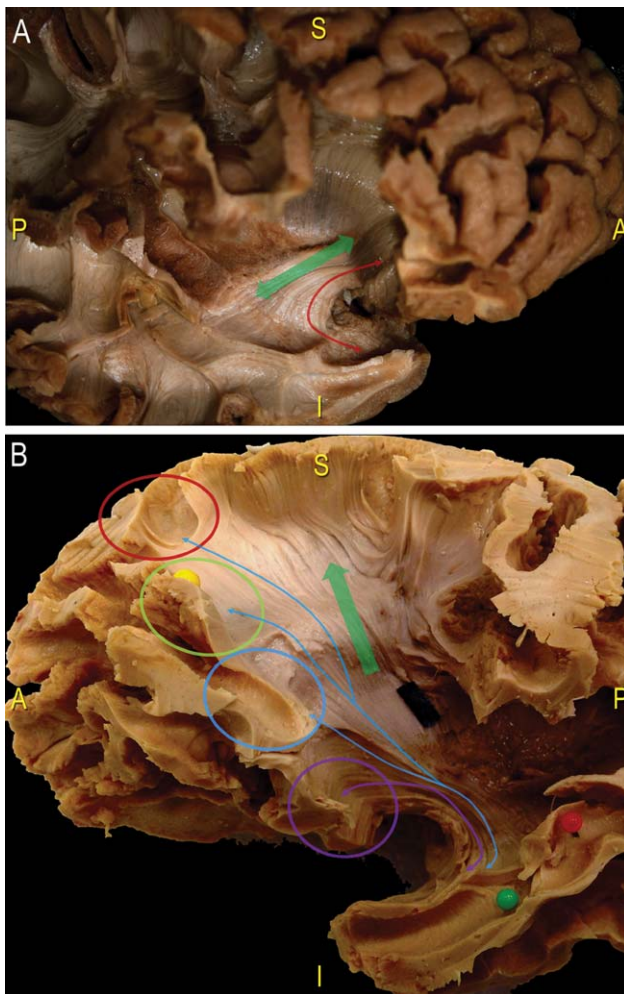


Figure 5.

In picture A, we showed the short lateral connections of the superficial layer of UF fibers. These fibers connect the IFG (particularly, PTri, and POrb) to the lateral cortex of the STG, the MTG, and the temporal pole. In picture B, we depicted: long fibers of the superficial component connecting the posterior and middle thirds of the SFG and the MFG (red and green circles, respectively) with the anterior temporal lobe; fibers of the “classical” deep portion of UF connecting the lateral and basal fronto-orbital (blue and violet circles) with the temporal pole. *Abbreviations:* EC: external capsule; MFG: middle frontal gyrus; MTG: middle temporal gyrus; PTri: pars triangularis; POrb: pars orbitalis; SFG: superior frontal gyrus; STG: superior temporal gyrus; UF: uncinate fascicle [Color figure can be viewed at wileyonlinelibrary.com]

investigation [Catani et al., 2013; De Witt Hamer et al., 2011; Duffau, 2015; Kinoshita et al., 2015; Maldonado et al., 2013; Makris et al., 2013]. Many recent studies have demonstrated that long- and short-range WM connections constitute the fundamental structural background of brain processing by providing a multimodal functional integra-

tion among different and distributed neural populations [Hosseini and Kesler, 2013; Skudlarski et al., 2008]. Even though it was recently hypothesized that WM actively mediates a possible reorganization of functional inputs through microstructural changes during short learning tasks [Tavor et al., 2013], a real capacity of structural restoration leading to functional recovery has not yet been demonstrated for human WM [Duffau, 2009]. Consequently, any damage to axonal pathways compromises the spatial and temporal synchronization between the cortical sites supporting any potential plastic reorganization [Duffau, 2014; van Geemen et al., 2014]. For these reasons, an accurate knowledge of the brain’s anatomical connectivity is the essential background to correctly understand and preserve these functions.

The “classical” dorsal stream is constituted of a multi-layer group of fibers, running around the circular sulcus of the insula (Figs. 2 and 3), and it includes the indirect anterior and posterior portions of the SLF and the AF. The two branches of the SLF run in a superficial layer of the WM, within the frontal and temporal lateral convexity. The indirect anterior SLF connects the VPMC and the posterior IFG (POp) (particularly the ventral and the posterior portion) to the anteroventral portion of the SMG and the AG (i.e., IPL) (Fig. 2a). The indirect posterior component of the SLF provides a mid-range and “tripod” connection between the posterodorsal portion of the IPL, the posterior temporal lobe and the most anterior mid-dorsal cortices of the occipital lobe (namely, the anterior MOG) (Fig. 2b). The AF runs in a deeper layer, in respect to these components of the SLF. The AF fibers are strongly paired with the deeper fibers of the indirect anterior component of the SLF, up to the AF stem at the temporoparietal junction. Even if the literature is not unanimous regarding the exact topography of the cortical terminations of the AF [Axe et al., 2013; Martino et al., 2013] and the connection subserved by the complex AF/SLF (particularly the indirect anterior component), we considered as pertinent to the AF all the fibers directly connecting the temporal and the frontal lobes (Fig. 3) and passing through the stem, also according to the classical anatomical definition of this tract. The AF/SLF system is considered as the anatomical background mediating the elaboration of auditory and somato-sensory inputs from the temporal lobe and the SMG and their conversion in working phonological-phonetic representations, which are then transferred to the VPMC to be translated into articulatory motor effectors [Catani et al., 2005b; Dick et al., 2014; Duffau, 2014]. Some Authors also hypothesized the involvement of the dorsal stream in complex syntactic processing during language comprehension [Brauer et al., 2013; Wilson et al., 2011]. Our anatomical data about the adjacent frontal terminations of AF and indirect anterior SLF match with functional results, showing that verbal apraxia and phonological paraphasias are paired at the level of the dorsal portion of the VPMC, and the most ventral portion of the posterior third of the MFG (Fig. 6).

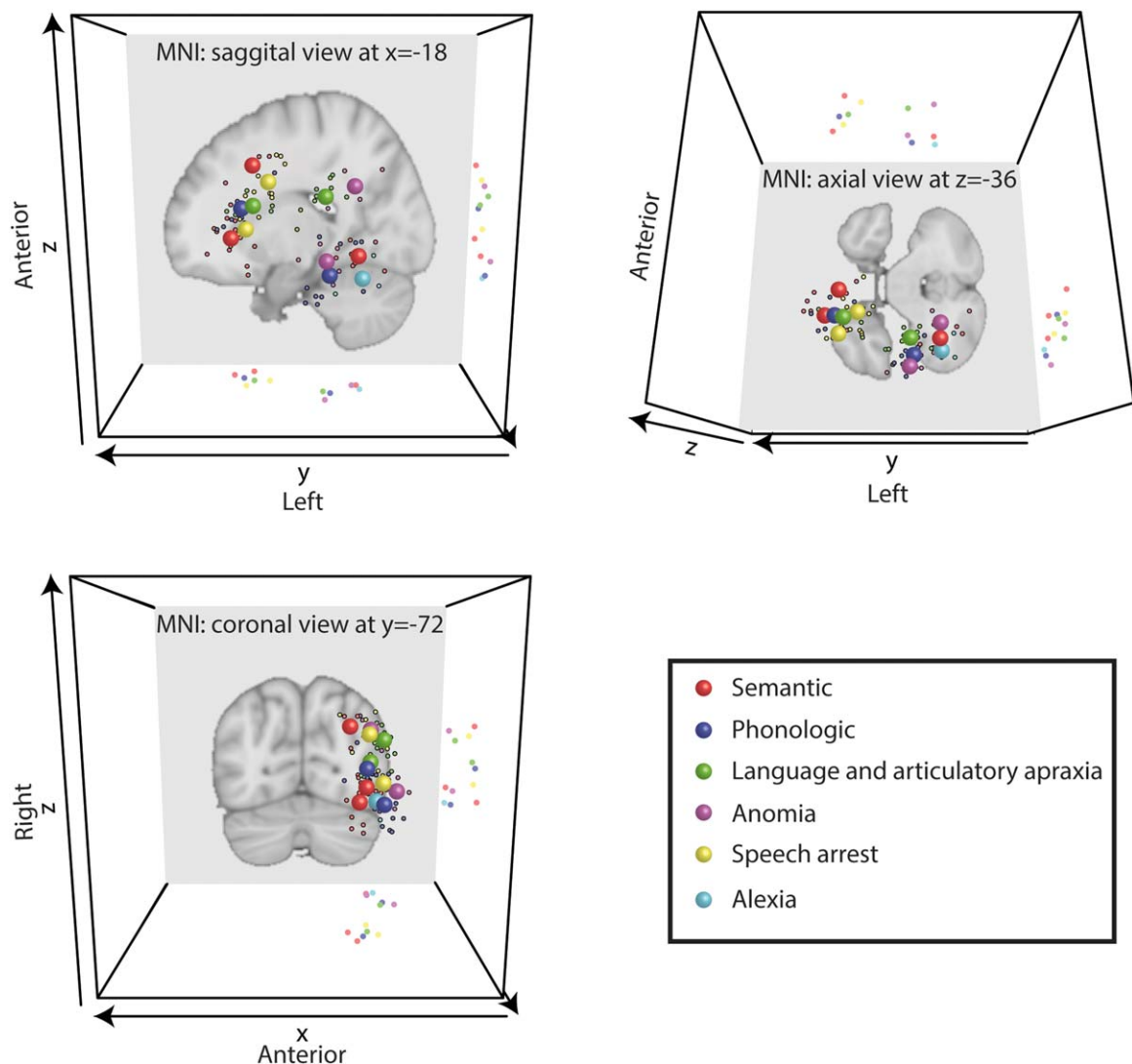


Figure 6.

Distribution of the main clusters (colored spheres) resulting from topographical analysis of the location of all the subcortical functional responses collected (colored points) in a 3D representation on the axial, sagittal and coronal planes of the MNI 152 (1 mm). Abbreviation: MNI: Montreal Neuroscience Institute. [Color figure can be viewed at wileyonlinelibrary.com]

Interestingly, we identified two main clusters of pure anomia. The first in the IPL, more dorsal and posterior in respect to verbal apraxia, and the second at the level of the posterior two thirds of the STG and the MTG, more dorsal and anterior in respect to phonological paraphasias (Fig. 6). From the structural point of view, the location of these functional responses suggests a possible important implication of the indirect posterior portions of the SLF (Figs. 2 and 6). Even if no defined data have been reported so far, our functional data suggest that the lateral WM of the temporoparietal junction is crucially involved in semantic retrieval and sensory-motor integration of

language elaboration. These functions could also be supported by the robust and direct short-range connectivity provided by U-fibers between the SMG/AG and the posterior third of STG.

The IFOF, UF, and ILF constitute the ventral semantic stream, running through the ventral and the medial WM of the occipital and the temporal lobe and within the most anterior portion of the EC, up to the frontal lobe. As the dorsal stream, the ventral pathway has also a bimodal direct/indirect organization. The IFOF has been demonstrated to have a major role in semantic processing, by providing direct communication between the occipital

visual area, the visual object form area, and the frontal executive processing [Duffau et al., 2005]. The UF and the ILF are considered as indirect components of the semantic system. The UF mainly connects the temporal to the frontal polar region, but extended termination territories have been described, including the orbital and lateral frontal cortices, the anterior cingulate gyrus anteriorly, and the amygdala, uncus, and parahippocampal gyrus, posteromedially. Similarly, in our specimens we found a wider distribution of UF fibers within the posterior lateral cortex of the MFG and the STG and a high degree of overlapping between the terminations of the superficial fibers of the UF and IFOF within the posterior frontal lobe. The effective participation of this tract in semantics is controversial and it probably concerns semantic memory retrieval and control of lower complexity data [Friederici et al., 2006; Jeffries and Lambon Ralph, 2006; Papagno et al., 2011].

Even if still debated, the ILF has been hypothesized to integrate occipital visual inputs with temporal limbic, memory areas, and frontal language territories, in association with the UF [Agosta et al., 2013; Catani and Thiebaut de Schotten, 2008; Duffau et al., 2008, 2013, 2014; Martino et al., 2011; Saur et al., 2008]. Interestingly, we found a cluster for alexia exclusively in the lateral WM of the posterior third of the ITS, around the cortical termination territories of the dorsal and lateral portion of the ILF and a third semantic cluster was found in the close proximity. This data confirm that this is a critical region for crossing between different pathways of the ventral stream. Moreover, recent stimulation data also support the interaction between the posterior portion of the ILF and the WM of the dorsal stream (namely the posterior part of the AF) in mediating the feedback between visual and nonvisual information during reading irregular and pseudowords [Zemmoura et al., 2015].

In this study, we provided anatomical and functional evidences in favor of a strong anatomo-functional integration, not only in the context of the WM pathways forming the ventral and dorsal subnetworks, but also between these two systems. The microdissections clearly demonstrated that deeper pathways (i.e., AF and IFOF) of both streams provide longer connection between more distant cortical territories. Conversely, shorter bundles (SLF branches, ILF, UF) have a more superficial course and connect closer cortices. This structural organization reflects a distinctive trait also of terminal fibers. Even if the analysis of termination sites demonstrated that adjacent bundles (i.e., in lateromedial direction) have adjacent terminations (i.e., in anteroposterior), the longest pathways (i.e., AF and IFOF) have a wider distribution (Figs. (2 and 3), and 5).

The analysis of short U-fiber connections also suggests a strict integration between different and specialized neural subpopulations within both frontal and temporoparietal cortices. Particularly, we found that the U-fibers form a homogenous and continuous layer between the ventral parietal region and the posterior two-thirds of the STG

and MTG (Fig. 1b), thus reinforcing the indirect (SLF) and direct (AF) connections between these regions and the frontal lobe. Moreover, our functional results revealed that the main clusters of pure anomia, verbal apraxia, and phonological paraphasia are tightly paired within the IPL and in the posterior temporal territories, indicating that the temporoparietal junction represents a crucial crisscross for the parallel semantic and sensory language processing, and for the integration of this information in the language planning (Figs. 2 and 6). These anatomical and functional results also confirm previous evoked-potentials data, which demonstrated a strong functional link between the peri-rolandic cortex, the posterior, basal and polar regions of the temporal lobe (output nodes), and the anterolateral frontal, superior parietal, and superior temporal regions (input nodes) [Keller et al., 2014].

Similarly to the AF and the SLF for the dorsal stream, the ventral pathways follow a parallel and paired architecture along their entire course, with the IFOF covered by the ILF and the UF, from the occipital lobe to the EC (Fig. 5). Moreover, termination sites of the ILF, UF, and IFOF matched with the location of alexia, semantic paraphasia, and pure anomia clusters, also within the ventral and basal cortices of the posterior temporal lobe. These results confirm that these regions are crucially involved in integrating different sensory inputs (i.e., visual, auditory, tactile) [Vandenberghe et al., 1996; Hickok and Poeppel, 2007; Stoeckel et al., 2003; Vigneau et al., 2006], beyond the classical definition of Wernicke's territories. Interestingly, the multimodal role of the left dominant IFOF has been recently proposed, after detecting its involvement not only in verbal semantic processing, but also in repetition of real words or pseudowords, proper name retrieval and awareness of self-knowledge during non-verbal tasks [Moritz-Gasser et al., 2013].

Finally, our data support the central role of the frontal region in language network. The primary implication of the frontal lobe in this circuitry has already been hypothesized by previous electrophysiological data based on cortico-cortical evoked potentials, showing that the stimulation of frontal language regions elicits stronger electrical responses in posterior language regions than vice versa [Keller et al., 2014; Matsumoto et al., 2004]. Moreover, we found a complete representation of all the main clusters of language components (i.e., semantic, phonological, articulatory, verbal planning, and execution) solely in the frontal lobe. From the structural point of view, excluding the two posterior indirect components of both the pathways (i.e., indirect posterior SLF and ILF, for dorsal and ventral stream respectively), we found that the other WM bundles have terminal fibers in the frontal area. In addition, a particularly strict anatomical integration between the dorsal and the ventral streams was evident in this region. In fact, the terminations of the indirect anterior SLF and the AF are strongly paired at the level of the VPMC (with a more anterior extension of AF, up to the POp) and of the MFG

(with a more anterodorsal extension of the AF). The main terminal territories of the AF are adjacent to the terminations of the superficial component of the IFOF (i.e., the most ventral portion of the PTri and the POrb) and to the deep IFOF fibers, specially at the level of the posterior third of the MFG. The adjacent UF fibers are more anterior in respect to the IFOF terminations within the ventral POrb and the fronto-orbito lateral cortex, and adjacent in the DLFPc. In this anatomical scenario, the serial connection provided by the horizontal U-fibers within the IFG seems to be particularly significant in the light of a possible cortical integration of a complex multimodal processing subserved by long pathways. Finally, the analysis of functional hubs distribution based on DES of the terminal fibers showed similar results. The semantics responses have a more anterior and ventral distribution within the IFG, whereas anarthria, verbal apraxia and phonological disturbances have a more posterior and posterodorsal location, respectively. These findings support the hypothesis of a semantic specialization of the ventral fibers (i.e., UF and IFOF) and the role of dorsal streams in phonological and articulatory processing (AF and indirect anterior SLF, respectively).

Limitations

Even if post-mortem dissections with cortex sparing technique is a reliable method for the identification of the termination territories and the whole course of long and short bundles, no methods are available to date for the neuroradiological co-registration of these findings with the functional evidences. Based on the above, a limitation of this study is related to the comparison of the anatomical location of the functional clusters with the results of the post-mortem dissections that was performed by an accurate visual comparison of the sulco-gyral anatomy of the specimens and of the reconstruction of the MNI 152 brain (1 mm) with the cortical ROIs of the JHU Atlas.

CONCLUSIONS

In this study, we highlighted the subcortical anatomico-functional organization of the language network, with the complementary use of post-mortem blunt microdissection and intraoperative brain mapping. We exposed the different WM pathways subserving the short and long-range connectivity between brain regions involved in the elaboration of inputs and executive aspects of language, according to the dorsal and ventral stream framework.

Terminations of the main language bundles and functional data demonstrated a wider distribution of eloquent cortices for language elaboration in respect to the classical definition of language territories. The dorsal and ventral streams were found to have a common anatomical layer organization. Even though the pathways of both the streams are strongly paired over their course, longer

bundles connect more distant cortices. Terminations of long- and mid-range bundles of dorsal and ventral streams are adjacent in the cortices of frontal, temporal, and parietal lobes, matching with the reciprocal distribution of the main subcortical functional clusters. Functional data and microdissections of language bundles showed how the anatomical and functional separation classically proposed for the dorsal and ventral streams is solved at the cortical level where terminations and subcortical functional responses are adjacent and paired. Finally, the anatomical analysis of the U-fiber revealed a structure supporting a locoregional strict integration between the different sub-networks, particularly in the IFG and at the temporoparietal junction.

ACKNOWLEDGMENTS

We are grateful to Ms. Paola Volpi for her precious support in the language revision of this manuscript. Conflict of interest: No one of the Authors has conflicts of interest. Funding: None.

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