An OP4 Functional Stream in the Language-Related Neuroarchitecture

Jorge Sepulcre1,2

1Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA and 2Athinioula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

Address correspondence to Jorge Sepulcre, Harvard University, 52 Oxford Street, Northwest Building, 280.02, Cambridge, MA 02138, USA.

Email: sepulcre@nmr.mgh.harvard.edu

Sensory comprehension and motor production of language symbols form the basis of human speech. Classical neuroanatomy has pointed to Wernicke’s and Broca’s areas as playing important roles in the integration of these 2 functions. However, recent studies have proposed that more direct pathways may exist between auditory input and motor output, bypassing Wernicke’s and Broca’s areas. We used functional network analyses to investigate potential auditory–motor (A–M) couplings between language-related cortices. We found that operculum parietale (OP) interconnectivity in region OP4 seems to play a critical role in the A–M integration of the brain. This finding supports a novel landscape in the functional neuroarchitecture that sustains language in humans.

Keywords: auditory–motor (A–M) interface, functional connectivity, graph theory, language, network

Introduction

Human verbal communication is based on the perception of sensory inputs and the selective use of speech motor signs. For more than a century, the arcuate fasciculus (AF) has been considered the main link between Wernicke’s and Broca’s areas, forming the structural foundation for the integration of language comprehension and articulation (Catani and fytche 2005; Catani and Mesulam 2008; Glasser and Rilling 2008; Friederici 2009; Turken and Dronkers 2011). Extensive studies of the human brain’s language network during the past decade, however, have revealed a more complex scenario. We now know not only that the tract anatomy of the AF is more diverse and more segmented than previously thought (Catani and Mesulam 2008; Glasser and Rilling 2008), but that other tracts also subserve the language system (Saur et al. 2008; Friederici 2009). In fact, the perisylvian language network includes both a dorsal stream, mainly comprising the AF and superior longitudinal fasciculus, and a ventral stream, composed of tracts such as the inferior longitudinal fasciculus, the extreme capsule, the uncinate fasciculus, and the inferior fronto-occipital fasciculus (Catani and Mesulam 2008; Glasser and Rilling 2008; Saur et al. 2008; Xiang et al. 2010).

Despite these recent advances in our knowledge, the brain network that sustains language in humans is still far from being fully understood. It has been suggested that the dorsal and ventral streams of the language network may have distinct functional properties (Wise et al. 2001; Hickok and Poeppel 2007; Rauschecker and Scott 2009; Hickok et al. 2011; Rauschecker 2011; Weiller et al. 2011; Rijntjes et al. 2012). The ventral stream connects the middle temporal gyrus with the pars orbitalis (F3Ob) and triangularis (F3Tr) of Broca’s complex and may play a role in lexical-semantic functions and mapping sound to meaning. Meanwhile, the dorsal stream, which connects posterior areas of the superior temporal gyrus with the pars opercularis (F3Op) and F3Tr of Broca’s complex, is thought to be associated with mapping sound to articulation. In this sense, the dorsal stream appears to be involved in sustaining auditory–motor (A–M) integration during speech (Hickok et al. 2009, 2011). However, one of the key unanswered questions is whether some A–M communications may bypass Wernicke’s and Broca’s streams to create straightforward sensory–motor integration. Specifically, speech abilities such as online error-monitoring, transfer of auditory-to-motor information, shadowing paradigms for the repetition of auditory–verbal stimulus, and pseudoword repetition have strongly suggested the existence of alternative or more direct pathways of communication between the primary auditory and motor cortices (Hickok and Poeppel 2007; Hickok et al. 2009, 2011). Although functional magnetic resonance imaging (fMRI) and lesion studies have pointed to the sylvian–parietal–temporal (Spt) area as playing an important role in A–M integration, other regions such as ventral premotor (vPM) or anterior insula beneath may also be involved (Dronkers 1996; Wilson et al. 2004; Warren et al. 2005; Hickok et al. 2009; Peschke et al. 2009). Based on the hypothesis that direct A–M communications should be reflected in the functional connectivity of the human brain, the goal of this study was to identify the functional streams and brain interfaces that integrate primary auditory and motor cortices by using novel MRI-based network connectivity methods.

Methods

Overview

Our overall workflow incorporated 3 distinct graph theoretical network methods based on resting spontaneous low-frequency (<0.08 Hz) blood oxygen level-dependent (BOLD) fluctuations (Biswal et al. 1995; Fox and Raichle 2007; Sporns 2013). Because it reflects polysynaptic and monosynaptic relationships between brain regions (Biswal et al. 1995; Fox and Raichle 2007; Lu et al. 2011), BOLD functional connectivity coupling allows identification of complex networks in the human brain. First, we used the network method known as stepwise functional connectivity (SFC) analysis (Sepulcre, Sabuncu, Yeo, et al. 2012) to characterize the main functional connectivity streams of the classically described language-related regions. Another analytical method known as network interconnection (NI) analysis was then used to reveal the pair-wise interconnectivity of specific brain targets (Sepulcre, Sabuncu, Yeo, et al. 2012). Finally, we performed hierarchical clustering (HC) analysis to describe the modularity pattern and network relationships between language-related regions of the human brain.
Participants
We analyzed a study dataset (n = 100, mean age = 21.3 year, 37% male) as well as 2 replication datasets (R1, n = 100, mean age = 20.83 year, 39% male; R2, n = 100, mean age = 21.16 year, 47% male) acquired from healthy young adult subjects recruited as part of a collaborative neuroimaging effort involving multiple laboratories at Harvard University, the Massachusetts General Hospital, and other institutions in the greater Boston area (Buckner et al. 2011). All subjects received compensation for their participation in the MRI studies. Inclusion criteria included no visible artifacts in the imaging data, no self-reported neurological or psychiatric illness, and history of psychoactive medications. Participants were native English speaking and right handed adults. All subjects had normal vision or corrected-to-normal vision. Participants provided written informed consent in accordance with the Declaration of Helsinki and the guidelines set by the institutional review boards of Harvard University and Partners Healthcare.

MRI Acquisition and Preprocessing
For each subject, we acquired high-resolution, 3-dimensional (3D), T1-weighted magnetization multi-echo structural images for an anatomical reference (multi-echo MPRAGE) as well as functional images using a gradient-echo echo-planar pulse sequence sensitive to BOLD contrast (Siemens, 12-channel phased-array head coil). The multi-echo MPRAGE parameters were: time repetition (TR) = 2200 ms, time to inversion = 1100 ms, time echo (TE) = 1.54 ms for image 1 to 7.01 ms for image 4, flip angle = 7°, 1.2 × 1.2 × 1.2 mm, and field of view (FOV) = 230. Echo planar imaging parameters were: TR = 3000 ms, TE = 30 ms, flip angle = 85°, 3 × 3 × 3 mm, FOV = 216, 47 slices, and 124 time points. MRI acquisition covered the entire brain. During the acquisition of functional data, participants were instructed to remain still, lying awake with their eyes open.

fMRI and fcMRI Preprocessing
MRI preprocessing steps were optimized for functional connectivity MRI analysis (Biswal et al. 1995; Fox et al. 2005; Buckner et al. 2009; Sepulcre et al. 2010). We first performed conventional fMRI preprocessing steps including removal of the first 4 volumes to compensate for T1-equilibration effects, motion correction, and normalization to the MNI atlas space (SPM2, Wellcome Department of Cognitive Neurology, London, UK) to yield a volumetric time series resampled at 2 mm cubic voxels. We then applied temporal filtering to the MRI data to remove constant offsets and linear trends over the data while retaining frequencies <0.08 Hz. We employed linear regression to remove several sources of spurious variance, along with their temporal derivatives, these included: (1) 6 parameters obtained from correction for rigid-body head motion, (2) the intensity signal averaged over the entire brain, (3) the intensity signal averaged over the body of the lateral ventricles, and (4) the signal averaged over white matter in the centrum semiovale. These functional connectivity MRI (fcMRI) preprocessing steps remove nuisance parameters that are unlikely to represent the signal of neuronal origin (Van Dijk et al. 2010), but can cause a shift in the distribution of the correlation coefficients and hence, make the interpretation of negative correlations ambiguous (Chang and Glover 2009; Murphy et al. 2009; Van Dijk et al. 2010). Therefore, only correlations that exceeded a positive were used in order to avoid negative correlations. The benefits as well as the drawbacks and limitations of fcMRI have been described previously (Van Dijk et al. 2010).

Network Analyses
Stepwise Functional Connectivity Analysis
The SFC analysis has been extensively described elsewhere (Sepulcre, Sabuncu, Yeo, et al. 2012). Briefly, we first obtained the association matrices corresponding to each subject’s whole brain network by computing the Pearson-R correlations of each voxel to every voxel time course of the BOLD images. To decrease the appearance of false positives, we used a multiple comparison correction method and only correlations that exceeded a false discovery rate (FDR)-corrected threshold (correction level <0.001) (Benjamini and Hochberg 1995) were included in the final analysis. SFC analysis was implemented using Matlab 7.4 (The MathWorks, Inc., Natick, MA, USA). Owing to computational efficiency reasons, we used down-sampled data of 4 (Fig. 2D) and 8-mm (Figs 1–3) isotropic voxel size, covering the entire brain and without gaps. The resulting adjacency matrices (undirected, unweighted graphs) served as the input data for the SFC analysis. Then, the degree of stepwise connectivity of a voxel \( k \) for a given link-step distance \( D(kj) \), is computed from the count of all paths that: (1) connect voxel \( j \) to any voxel in the target area \( i \) and (2) have an exact length of \( l \). In this sense, a link-step distance refers to the number of links belonging to a path that connects a node to the target region. As illustrated in Figure 1A, the SFC analysis is a graph theory method that computes the degree of connectivity (represented by node size) between brain voxels and a target region (dark blue nodes) at different link-step distances (Sepulcre, Sabuncu, Yeo, et al. 2012). Our studies of SFC analysis have demonstrated the sensitivity of this method for detecting not only direct connectivity, but also distributed connectivity to more distant relevant brain regions (Sepulcre, Sabuncu, Johnson 2012; Sepulcre, Sabuncu, Yeo, et al. 2012), thus allowing the progressive, multistep visualization of functional streams.

It is important to note that fcMRI does not provide directional information and SFC analysis can account for recurrent crossings of pathways across the target regions. Moreover, resting-state fcMRI data SFC shows spatial stability after a certain number of link-step distances (Sepulcre, Sabuncu, Yeo, et al. 2012). In this sense, the line graphs in Figure 1B show voxel-by-voxel spatial correlations of consecutive pairs of SFC maps (examples are obtained from the SFC maps of Broca’s complex component F3R—top—and Wernicke’s area—bottom). This approach was used as a proxy to analytically check the topological similarity and spatial stability of the maps. The stable state was evident when similarity of maps—measured by voxel-by-voxel spatial correlations—reached Pearson coefficients of \( r > 0.999 \) (Fig. 1B; and cortical maps on the right in Fig. 1D). The cortical maps reached a stable state that collapsed into regions now considered to be the cortical hubs of the human brain. The cortical hubs are the regions with the greatest number of functional connections to other areas of the brain and seem to be at the top of the brain hierarchical structure (Buckner et al. 2009; Sepulcre et al. 2010). As Figure 1B shows, before reaching topographical stability, stepwise cortical maps display different amounts of overlap and similarity with one another. Figure 1D and Supplementary Figure 1A,C show representative transitions of the SFC maps to avoid redundancy. Importantly, to achieve statistical significance in our SFC maps, we used the entire sample of individuals to obtain one-sample z-score transformed maps (the significance level of right-tailed \( P \)-value of <0.005 is reported).

Interconnections Between Pairs of Cortical Regions
The NI analysis is used to identify brain voxels that directly link 2 target brain regions (Fig. 2A; Sepulcre, Sabuncu, Yeo, et al. 2012). Although SFC analysis can distinguish the connectivity streams between a given region of interest (ROI) and the rest of the brain in a stepwise manner, it does not allow direct calculation of the interconnectivity between a pair of regions, through a third relay station. NI analysis can complete the SFC results, detect interconnections, and estimate the degree of interconnectivity between 2 brain regions. First, voxel nodes (voxel \( k \)) with direct connectivity in one link-step distance to “both” target regions \( (a \land b) \) are selected; the degree of interconnectivity of a voxel \( k (Dk) \) can then be computed from the number of links connecting voxel \( k \) to other voxels in target regions \( a \) and \( b \). Similarly to the SFC maps, we used the entire sample of individuals to obtain one-sample z-score transformed maps (the significance level of right-tailed \( P \)-value of <0.005 is reported).

Both NI and fcMRI seed-based conjunction analyses can detect common areas of connectivity between brain regions. However, whereas NI computes the degree of connectivity from the interconnectivity region to target nodes, conjunction analysis computes the binary or correlation strength overlap of 2 seed-based maps.

Potential Spatial Confounds in the Network Interconnectors Analysis
To control for the possible impact of partial volume or spatial closeness effects on the detection of auditory and motor cortex interconnectivities, we used 2 strategies. First, we used NI analysis with and without
Gaussian smoothing during MRI data processing (Fig. 2B, I). In both cases, in order to increase spatial separation between targets, we examined images with a higher spatial resolution (4-mm isotropic voxel size) than for the original analyses. Secondly, we hypothesized that if there is a bleeding of signal crossing the sylvian fissure between the auditory and motor cortices, this phenomenon should not be restricted only to those 2 areas, but affecting other regions along the entire fissure. In other words, if our findings are due to nonspecific couplings between nearby signals, then other pairs of ROIs that are placed across both sides of the sylvian fissure should show the same bias. We performed several additional NI analyses using parallel and equidistant pairs of ROIs to test this possibility (Fig. 2B, I). To rule out this important concern, we considered a P-value cutoff of <0.001.

Regions of Interest
Identification of the language-related brain regions has long been a challenge to the neuroscience community (Grodzinsky and Santi 2008). The SFC and NI analyses we used in this study focused on ROIs defined by the earlier literature and classic anatomical landmarks (see Fig. 1C for detailed illustration of the ROIs in Figs 1 and 2). The respective Montreal Neurological Institute (MNI) coordinates (X, Y, Z) for each of ROIs used in the SFC and NI analyses were: F3Tr (−50, 22, 12) (Tzourio-Mazoyer et al. 2002; Goulas et al. 2012; Tomasi and Volkow 2012), F3Or (−50, 30, −12) (Tzourio-Mazoyer et al. 2002; Tomasi and Volkow 2012), F3Op (−50, 6, 4) (Tzourio-Mazoyer et al. 2002; Goulas et al. 2012), Wernicke’s area (−50, −42, 12) (Wise et al. 2001; Tomasi and Volkow 2012), motor tongue/mouth (−50, −10, 36 and 54, −10, 36) (Backner et al. 2011; Price 2012), primary auditory (−50, −18, −4 and 54, −18, −4) (Eickhoff et al. 2005; Sepulcre, Sabuncu, Yeo, et al. 2012), and Spt (−50, −42, 20) (Hickok et al. 2009). Broca’s complex was examined in its entirety including all of its 3 components, namely F3Tr (Fig. 1D and Supplementary Fig. 1A, C), F3Or (Fig. 1D), and F3Op (Fig. 1D). As for the Wernicke’s area, its classical description as located in Brodmann area (BA) 22 and the posterior portion of the superior temporal gyrus was critical in the selection criteria for this ROI (Fig. 1D and Supplementary Fig. 1A, C). We adapted the MNI coordinates extracted from the literature to fit our voxel size and volume space. All

Figure 1. (A) illustrates a diagram of the SFC method. The size of nodes represents the degree of connectivity at specific link-step distances (also refer as LSD in D). (B) shows line graphs of the pair-wise similarity/stability analysis (voxel-by-voxel spatial correlations of consecutive pairs of SFC maps). Star symbols in similarity/stability analysis point to examples of transitions between dissimilar (*) and similar (**) maps. (C) shows the ROIs used in the study. (D) shows the stepwise connectivity maps of Broca’s complex (F3Tr, F3Or, and F3Op) and Wernicke’s area. Color scales are normalized z-scores of stepwise degree of connectivity values. Red color always represents P-values of <0.005. Blue nodes in D represent the target regions under the study.
the ROIs we examined were equal-sized cube regions of 8 voxels (in both 8 and 4 mm images), which allowed us to (1) compare the degree of connectivity in the maps from different targets and (2) acquire graded rather than binary results in the one-step distance SFC and NI methods (Sepulcre, Sabuncu, Yeo, et al. 2012).

Hierarchical Clustering Analysis

We performed HC analysis to examine the modularity structure and specific relationships of the main language-related brain regions. HC analysis was based on (1) the averaged functional connectivity data obtained from the original FDR-corrected association matrices of subjects (dataset R1) and (2) previous ROIs from F3Tr, Wernicke's area, motor tongue/mouth, primary auditory cortex, and Spt as well as new ROIs defined from the results of the SFC and NI analyses [operculum parietale 4 (OP4) (−50, −10, 20; Fig. 2B, I), F3Op/vPM (−58, 6, 4; Fig. 2B, V), mid-frontal (−42, 14, 44; letter a in Figs 1D and 2B, I), and mid-temporal (−58, −34, −4; letter c in Figs 1D and 2B, I)]. Finally, we performed an HC analysis in the association matrix using the Cluster software (Cluster v3.0, 1988, Stanford University), the average-linkage method, and stringent cluster cutoff criteria of $r > 0.4$.

Visualization

As a final step, all cortical maps were projected onto the cerebral hemispheres of the PALS surface (PALS-B12), provided with the Caret software (Van Essen and Dierker 2007) using the “enclosing voxel algorithm” and “multifiducial mapping” settings. To aid visualization, we used a z-score transformation of the SFC and NI degree connectivity results and displayed the positive z-score values using an intensity-normalized color scale (minimum = 0 and maximum = 1) in Caret (Van Essen and Dierker 2007). We used the Pajek software (De Nooy et al. 2005) to display the network graphs (Kamada–Kawai energy layout) (Kamada and Kawai 1989), as shown in Figures 1A and 3A.

Results

Main Functional Streams of Classical Language-Related Areas (Broca’s Complex and Wernicke’s Area)

In the first step of our analysis, we investigated the functional streams of the classical language-related regions of Broca’s

Figure 2. (A) shows a diagram of the network interconnectors method. (B) shows the results of the network interconnectors analysis between target regions. Star symbols (*) in magnified figures mark the maximum peak of the degree of interconnectivity value in OP4. Blue nodes in B represent the target regions under the study. (C) is the probabilistic map of OP4 from Amunts et al. (2007). (D) shows the values of the degree of interconnectivity in OP4 region from 4 different analyses: auditory and motor, Wernicke and motor, Spt and motor, as well as Broca F3Tr and motor. Color scales are normalized z-scores of the stepwise degree of connectivity values. Red color always represents P-values of <0.005. A P-value in (D) is computed by using a paired t-test between left and right OP4 from the auditory and motor maps.
complex and Wernicke’s area. At one link-step distance, F3Tr in Broca’s complex displays strong functional connectivity to the mid-frontal (Fig. 1D, letter a), parieto-temporal (Fig. 1D, letter b), and mid-temporal (Fig. 1D, letter c) regions. This connectivity pattern that we observed agrees well with previous descriptions of the cortical regions involved in the dorsal and ventral streams of human language (Catani and Mesulam 2008; Glasser and Rilling 2008; Saur et al. 2008; Xiang et al. 2010). At the local level, F3Tr is tightly connected to both F3Op and F3Or. More distantly, however, F3Tr functional connectivity merges with that of a set of regions that are now known as the main connectivity hubs of the human brain (Buckner et al. 2009; Sepulcre et al. 2010; Sepulcre, Sabuncu, Johnson 2012). In contrast, F3Or shows a more direct and intimate coupling to these hubs compared with F3Tr. As shown in Figure 1D (letters d, e, and f), SFC maps of F3Or do not change across connectivity steps and remain stable in the cortical hubs topology. Interestingly, F3Op connects to vPM/anterior insula and the ventral OP—particularly, area OP1—(Fig. 1D, letters g, h), in a similar way as Wernicke’s area does (Fig. 1D, letters i, m). However, Wernicke’s area shows important differences. Wernicke’s area connects locally with auditory-related brain regions (Fig. 1D, letter i) including Spt and, to a lesser extent, the area OP4 (BA 43) (Fig. 1D, letter j) and primary motor cortex (Fig. 1D, letter k). Subsequent analysis steps reveal that the Wernicke’s area connectivity stream also reaches the cortical hubs.

**OP4 Has Auditory–Motor Interconnector Properties in the Human Brain**

Our finding that Wernicke’s area connects to both OP4 and the motor strip (Fig. 1D, letter j and k) is not only intriguing, but also points to the possibility that sensory–motor communications may follow an OP-related pathway. To directly test this prospect, we used a second network analysis to determine interconnections between pairs of language-related regions (Fig. 2A and blue bar in Fig. 2D). First, NI analysis of the motor and auditory cortices (targeting the tongue-mouth area and the primary auditory cortex) showed direct interconnectivity through OP4 (Fig. 2B, I). Additional analyses with Gaussian smoothing (GS; Fig. 2B, I) and without GS (Fig. 2B, I, NGS) during image preprocessing of the 4-mm voxel size data confirmed that functional connectivity from the primary motor and auditory cortices converges in OP4. Of note, the nonsmoothed results showed medial displacement of the maximum peak in OP4 (Fig. 2B, I, NGS), which also covers OP3 and a small portion of the insula (see Amunts et al. 2007; Burton et al. 2008; Zilles and Amunts 2010 and Fig. 2C for OP4 anatomical references). We also confirmed that, compared with other parallel pairs of parasylvian ROIs, the NI analysis using the primary auditory and motor pairs was the only combination that had significant results in a parasylvian region (Fig. 2B, I, pair number 3). Interestingly, the OP4 region is not only the third relay station between auditory and motor cortices, but also, although to a lesser extent, between Wernicke’s area versus...
motor cortex (Fig. 2B, III and black bar in Fig. 2D) and Spt versus motor cortex (Fig. 2B, IV and dark gray bar in Fig. 2D).

On the other hand, F3Tr and the primary motor cortex are interconnected through the F3Op/vPM areas, as well as part of the anterior insula cortex, where OP4 appears to have a lesser role (Fig. 2B, V and light gray bar in Fig. 2D). These data, therefore, suggest that the F3Op/vPM area, but not OP4, may serve as the main pathway between Broca’s F3Tr and final motor outputs. Moreover, OP4 does not play a role in connecting Broca’s F3Tr and Wernicke’s area (Fig. 2B, II). Finally, we found that OP4 exhibits stronger A–M interconnectivity in the left hemisphere than in the right (red and green bars in Fig. 2D).

To achieve consistent findings, we replicate the SFC and NI analyses in 2 additional samples; dataset R1 (Supplementary Fig. 1A,B) and R2 (Supplementary Figure 1C,D). Congruently with our previous results, Supplementary Figure 1A,C shows the replication of the stepwise connectivity maps of Broca’s F3Tr and Wernicke’s area, and Supplementary Figure 1B,D also shows the replication of the auditory–motor interconnectivity.

**Functional Modules in the Language-Related Neuroarchitecture**

We used modularity analysis to understand the network structure of the language-related neuroarchitecture and to estimate the role of OP4 within the overall functional relationships between these brain regions. For this step, we selected the language-related ROIs based on the results shown in Figures 1D and 2B (see Methods section for details). The results of modularity analysis show 2 very distinct network modules: one that comprises Wernicke’s area, the primary motor tongue/mouth cortex, primary auditory cortex, OP4, and F3Op/vPM (module a and green nodes, Fig. 3A), and a second that includes F3Tr and Spt regions as well as mid-temporal and mid-frontal areas (module b and blue nodes, Fig. 3A). Importantly, only 3 regions, all mainly belonging to one particular module, share their nodes with both the a and b modules (red arrows, Fig. 3A). In other words, Wernicke’s area (pink nodes, Fig. 3A), Spt (white nodes, Fig. 3A), and F3Op/vPM (black nodes, Fig. 3A) appear to merge the overall language network by connecting modules a and b, whereas OP4 is well confined within the module a (brown marked nodes, Fig. 3A).

**Discussion**

Human language is a high-level cognitive function supported by a set of distributed and dynamically interconnected brain regions. Over many years, detailed studies of the neuroanatomy and structural connectivity of the language-related regions have revealed, distinct ventral and dorsal streams, each composed of several white matter bundles, that have provided a framework for understanding the language network (Kaas and Hackett 2000; Hickok and Poeppel 2007; Catani and Mesulam 2008; Glasser and Rilling 2008; Friederici 2009; Weiller et al. 2011; Rijntjes et al. 2012). Brain regions outside the classical left-sided Broca’s complex and Wernicke’s area, such as the temporoparietal junction, anterior and middle temporal cortex, anterior insula, subcortical regions, and cortical right-hemisphere homologues, have also been identified as having a role in language processing (Damasio and Damasio 1980; Dronkers 1996; Hickok and Poeppel 2007). Our study builds upon these discoveries, focusing on functional coupling between brain areas, to identify direct A–M interconnections. Toward this goal, we incorporated distinct but complementary analytical approaches to detect streams of connectivity between regions and modules of the language-related network.

The results of the SFC analysis show that classical language areas exhibit different connectivity patterns to distributed brain regions. For instance, the triangularis of the Broca’s complex has strong and direct functional connections to specific frontal, parietal, and temporal areas that have been characterized as the main dorsal and ventral language-processing streams (Rilling et al. 2008; Saur et al. 2008; Hickok et al. 2011). In contrast, except for its local association with F3Tr, the orbitalis part of Broca’s complex does not exhibit connectivity to the dorsal and ventral language stream regions. Rather, this region is directly connected to a set of high-order cognitive regions that are thought to be hubs at the top of the brain hierarchy (Mesulam 1998; Buckner et al. 2009; Sepulcre et al. 2010; Sepulcre, Sabuncu, Yeo, et al. 2012). On the other hand, the opercular of Broca’s complex features a main functional stream through a specific network that has been described previously as a multimodal sensory–motor integration network (Downar et al. 2000; Yeo et al. 2011; Goulas et al. 2012; Sepulcre, Sabuncu, Yeo, et al. 2012). Therefore, the main streams of connectivity of the Broca-related regions suggest that whereas F3Tr may represent the more conventional “language-related network,” F3Or makes a part of the cortical hubs system, while F3Op belongs to a multimodal integration network. In this context, we could speculate that F3Or plays a pivotal network role in connecting the F3Tr-related language network with the cortical hubs, specifically, given its extensive connectivity to the middle temporal gyrus, through a ventral stream, whereas F3Op may play an important network role in connecting the F3Tr-related language network with the distributed neural systems that integrate motor and multimodal information. Similarly to previous tractographic investigations (Frey et al. 2008), we found that F3Tr and F3Op have dissociated pathways in the language-related network. F3Tr connects to the network via dorsal and ventral streams, whereas F3Op only connects via dorsal streams. In the past, F3Tr—and its connectivity through the arcuate fascicle (Rilling et al. 2008)—has been related to highly unique human language functions such as syntax processing (Musso et al. 2003). In this sense, our findings challenge the idea that syntax functions are exclusively supported by dorsal streams.

The stepwise connectivity maps of Wernicke’s area showed relevant connections to the surrounding auditory-related cortex and, like F3Op connectivity, to multimodal integration regions. However, the most notable finding was the connections between Wernicke’s area to OP4 and the motor strip—invoking motor areas associated with movement of the tongue, mouth, and larynx, as well as speech vocalization (Penfield and Roberts 1959; Bouchard et al. 2013). These findings introduce a fascinating possibility, that is, the possible existence of more straightforward communications between sensory-related and primary motor regions, without mediation by the classically defined dorsal and ventral language streams. The NI analysis showed that OP4 directly interconnects the sensory areas of the temporoparietal region with the primary motor cortex. Part of the mid-perisylvian cortex (BA 45), OP4 is located in the ventral part of the somatomotor strip. Classical human
neuropsychological studies showed that intra-cortical electrical stimulation of OP4 might produce a variety of speech phenomena such as stop, arrest, slurring, hesitation, distortion, or repetition of language (Penfield and Roberts 1959). Moreover, past functional and structural imaging studies have described that OP4 has an important role in several language processes. For instance, positron emission tomography neuroimaging and meta-analysis studies have suggested that OP4 is related to word repetition and verbal articulation functions in Petersen et al. (1988) and Price (2012). Other groups have also noted the key roles that the secondary somatosensory and parietal operculum areas play in sensory–motor integration in the context of bilingualism (Simmonds, Wise, Dhanjal, et al. 2011; Simmonds, Wise, Leech 2011), or in online sensory monitoring of outputs during utterance (Guenther et al. 2006). Furthermore, significant variations in the gyral anatomy of BA 43 and disruptions of the juxtacortical white matter in the OP4 region have been extensively reported in subjects who suffer from fluency articulation problems such as stuttering (Foundas et al. 2001; Sommer et al. 2002; Buchel and Sommer 2004).

At the tract anatomical level, 2 elegant studies have already studied in great detail the structural connectivity of OP4 (Eickhoff et al. 2010; Ro et al. 2013). Eickhoff et al. (2010) have demonstrated the existence of strong connections between OP4 and primary motor cortex, whereas Ro et al. (2013) have described the tracts connecting OP4 and primary auditory cortex. Moreover, it is not surprising that recent imaging studies in humans have suggested that the ventral somatomotor cortex, including OP4, forms a strong functional module with the auditory cortex (Yeo et al. 2011; Sepulcre, Sabuncu, Yeo, et al. 2012). In summary, these findings strongly support that OP4 may mediate the connectivity integration of primary motor and auditory-related regions in the human brain.

In recent years, several groups have proposed that the language-related architecture includes lower-order sensory–motor interfaces that support, among other speech abilities, fast error-monitoring feedback during speech development in children, as they learn to articulate speech, or pseudoword repetition in adults (Warren et al. 2005; Peschke et al. 2009; Hickok et al. 2011). These speech abilities may not involve mediation by the semantic-related systems of the brain and have generated a great deal of speculation about the potential existence of lower-level systems for sensory–motor processing that bypass Wernicke’s area or Broca’s complex. For instance, children likely learn to speak through imitation, by gradually building sensory and motor fingerprints of words without associating them to meaning (Weiller et al. 2011; Rijntjes et al. 2012). In this sense, if the functional connectivity profile of a brain region is related to the actual function during task performance, OP4 may be a good candidate for these developmental sensory–motor fingerprints in bimodal association cortices.

Spt has been proposed as holding prominent A–M integration functions (Hickok et al. 2009). In our findings, Spt, along with Wernicke’s areas, connects to the motor strip via OP4. Moreover, Spt, in conjunction with F3Op/vPM and Wernicke’s area, links the sensory–motor module (green nodes in Fig 3) with the classically defined language-related module (blue nodes in Fig 3) to form a complete network, suggesting that Spt plays an important role in merging key network modules of the language-related neuroarchitecture (see Supplementary Fig. 1B). In this sense, the transfer of sensory–motor information may take place not only at the lower level within the OP4/sensory–motor module, but also at the higher level, between both network modules, through the intermediate regions such as Spt, F3Op/vPM, and Wernicke’s area.

The present study shows that OP4 may play a substantial role in integrating functional coupling between the primary auditory and motor regions. The methods we employed aimed to describe A–M interfaces in the context of the complex structure of the language-related network. However, because subjects were examined at rest, it is difficult to interpret the exact function of OP4 during language- or speech-specific task. As previously noted, several studies have suggested that OP4 may be related to several language functions and fluency deficits, but further investigation is needed to understand the implication of this region in human speech. Another key question is whether the OP4, as well as the sensory–motor module, acts independently or in parallel with the ventral and dorsal streams of the human language network. That is, it is possible that the merging of A–M connections in OP4 complements the dorsal language stream during speech functions. Alternatively, OP4 may also be part of any of another auditory stream (Rauschecker 2011) or may even act as an independent route in sensory–motor language processing. Finally, OP4 functional connectivity to the primary auditory and motor areas must be interpreted as both monosynaptic and polysynaptic; therefore, other relay stations, such as the subcortical regions (see for instance Lehericy et al. 2004; Booth et al. 2007), may play a significant role in the overall interconnectivity pattern.

Notes

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References

Fox MD, Raichle ME. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 8:700–711.