

Parcellation-based modeling of the supplementary motor area

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ABSTRACT

Introduction: The supplementary motor area (SMA) plays an important role in the initiation and coordination of internally and externally cued movements. Such movements include reaching, grasping, speaking, and bilateral hand coordination. While many studies discuss the SMA and its relationship to other parts of the motor network, there is minimal literature examining the connectivity of the SMA outside of the motor network. Using region-based fMRI studies, we built a neuroanatomical model to account for these extra-motor connections.

Methods: Thirty region-based fMRI studies were used to generate an activation likelihood estimation (ALE) using BrainMap software. Cortical parcellations overlapping the ALE were used to construct a preliminary model of the SMA connections outside the motor network. DSI-based fiber tractography was performed to determine the connectivity between cortical parcellations. The resulting connections were described using the cortical parcellation scheme developed by the Human Connectome Project (HCP).

Results: Four left hemisphere regions were found to comprise the SMA. These included areas SFL, SCEF, 6ma, and 6mp. Across mapped brains, these areas showed consistent interconnections between each other. Additionally, ipsilateral connections to the primary motor cortex, left inferior and middle frontal gyri, the anterior cingulate gyrus, and insula were demonstrated. Connections to the contralateral SMA, anterior cingulate, lateral premotor, and inferior frontal cortices were also identified.

Conclusions: We describe a preliminary cortical model for the underlying structural connectivity of the supplementary motor area outside the motor network. Future studies should further characterize the neuroanatomic underpinnings of this network for the purposes of medical application.

1. Introduction

The supplementary motor area (SMA) coordinates fundamental aspects of human motor planning [1]. The SMA is well known to assist in the initiation and coordination of internally motivated movements [2–6]. This includes limb movement as well as the motion related to speech production [2,4,7–9]. The SMA has also been implicated in coordinating externally cued movements, such as reaching and grasping for a visible object [10–13]. It is also involved in the timing and sequential ordering of bilateral extremity tasks [6,7,12,14–17], balancing movement initiation and inhibition in order to produce a fluid and situationally appropriate motion [18].

While several studies present a clear picture of the functional

significance of the SMA, few have yet to demonstrate a complete anatomical map of the supplementary motor area and its cortical projections. In particular, previous studies on the human SMA have been completed in a variety of atlas schemes, and we aim to describe the SMA in a parcellation scheme that is scalable to be able to use with machine learning in the future [19,20]. Further, extra-network connections between the motor system and other areas of the cortex are of particular interest as they may explain how the motor system modulates cerebral activity beyond motor function.

In this study, we constructed a model of the SMA based on the cortical parcellation scheme published under the Human Connectome Project (HCP) [21]. Using relevant task-based functional magnetic resonance imaging (fMRI) studies and BrainMap (<http://www.brai>

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nmap.org/), a collection of open-access software programs used to generate activation likelihood estimations from fMRI studies, we have identified the key cortical areas involved in the SMA [22–25]. After identifying these regions of interest, we performed DSI-based fiber tracking to determine the structural connectivity between parcellations, both within and without the motor network. Our goal is to provide a more detailed anatomic model of the connections of the SMA for use in future studies.

2. Methods

2.1. Literature search

We searched BrainMap Sleuth 2.4²⁴ on July 20, 2017 for all relevant task-based fMRI studies related to the supplementary motor area. To precisely identify studies connecting SMA motor activity to other cortical areas, we used a region of interest (ROI) search algorithm related to the SMA as opposed to searching for studies related to motor

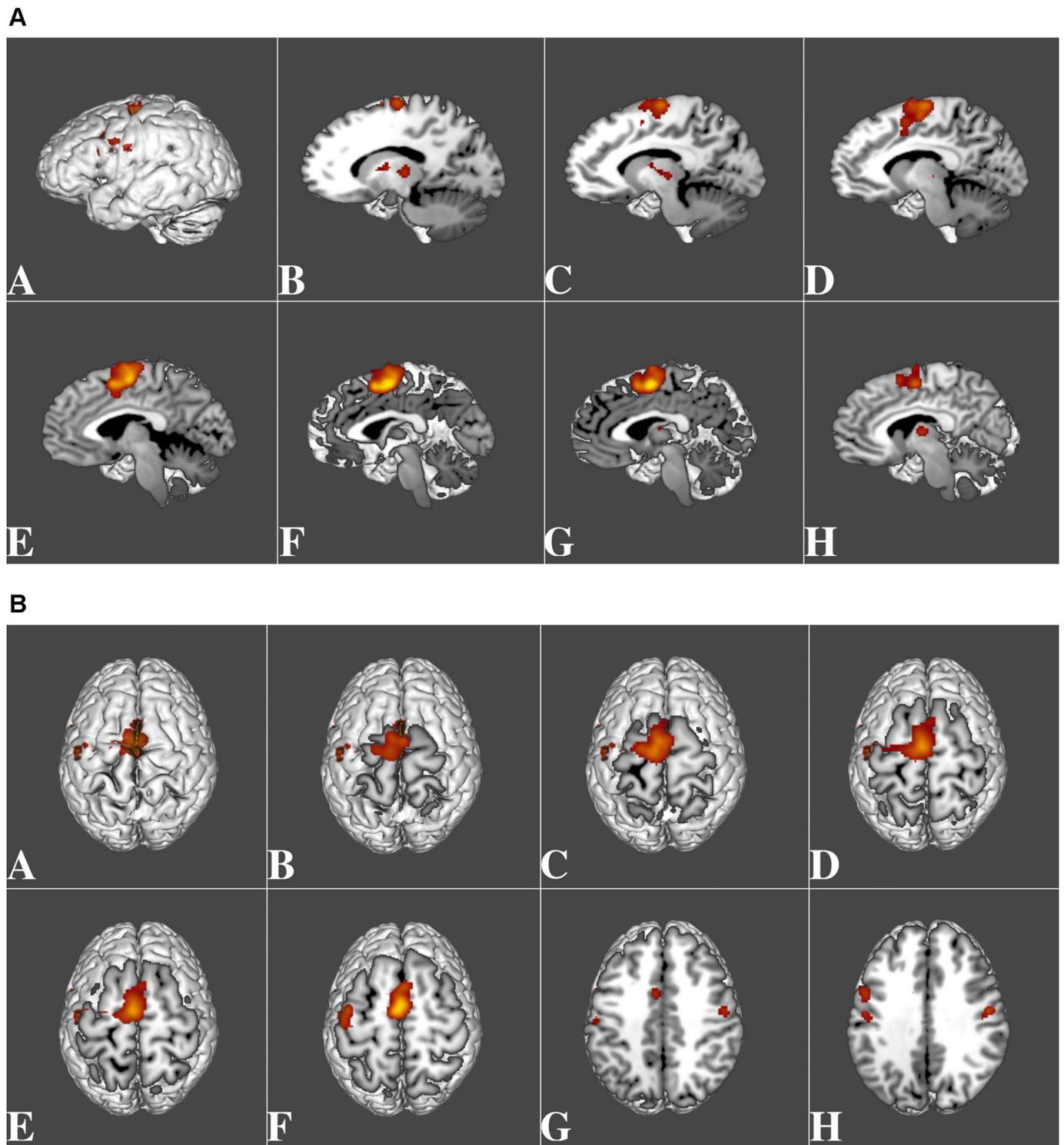


Fig. 1. Representative (a) sagittal (b) axial images on a sample MNI brain showing the ALEs in the study.

Table 1

Name and abbreviations of the parcellations involved in the supplementary motor area.

Parcellation abbreviation	Parcellation name
SFL	Superior Frontal Language area
SCEF	Supplementary and Cingulate Eye Field
6ma	Brodmann Area 6 medial anterior
6mp	Brodmann Area 6 medial posterior

function. Studies were included in our analysis if they met the following criteria: (1) peer-reviewed publication, (2) task-based fMRI study related to the SMA cortex, (3) based on whole-brain, voxel-wise imaging, (4) including standardized coordinate-based results in the Talairach or Montreal Neuroimaging Institute (MNI) coordinate space, and (5) including at least one healthy human control cohort. Only coordinates from healthy subjects were utilized in our analysis. Resting state studies were excluded from our subsequent analysis. Overall, 30 papers related to the SMA met criteria for inclusion in this study [5,26–54].

2.2. Creation of 3D regions of interest

The three-dimensional ROIs used in this study were generated from data previously published by the HCP authors [21]. In their study, the authors used surface-based greyordinates to study 180 cortical ROIs in CIFTI format. CIFTI files use a surface-based coordinate system, termed greyordinates, to localize ROIs on inflated brains [21]. This is in contrast to traditional file formats which denote ROIs based on volumetric dimensions [55]. As a result, it was difficult to overlay HCP areas onto anatomic scans and perform diffusion spectrum fiber tractography. To convert the HCP parcellation data to NIFTI-based volumetric coordinates, we used the Connectome Workbench Command, a program consisting of command line tools used to perform simple and complex operations within Connectome Workbench [56]. The method we used is similar to those performed by others [57] and involves the following steps: 1) the vertex label files were downloaded from the BALSAs website, 2) the surface meshes “L.sphere.32k_fs_LR.surf.gii”, “R.sphere.32k_fs_LR.surf.gii”, “fs_L/fs_L-to-fs_LR.fsaverage.L_LR.spherical_std.164k_fs_LR.surf.gii” and “fs_R-to-fs_LR.fsaverage.R_LR.spherical_std.164k_fs_LR.surf.gii” from the HCP Github at https://github.com/Washington-University/Pipelines/tree/master/global/templates/standard_mesh_atlases, 3) we then created individual hemisphere label files from the Dlabel.nii files from the BALSAs website using the following commands: `wb_command - cifti separate Q1-Q6_RelatedParcellation 210.L.CorticalAreas_dil_Colors.32k_fs_LR.dlabel.nii COLUMN -label CORTEX_LEFT Q1-Q6_RelatedParcellation210.L.CorticalAreas_dil_Colors.32k_fs_LR.label.gii` and `wb_command - cifti-separate Q1-Q6_RelatedParcellation210.R.CorticalAreas_dil_Colors.32k_fs_LR.dlabel.nii COLUMN -label CORTEX_RIGHT Q1-Q6_RelatedParcellation210.R.CorticalAreas_dil_Colors.32k_fs_LR.label.gii`, 4) we then utilized the connectome workbench to resample the label files as follows: `wb_command -label-resample Q1-Q6_RelatedParcellation210.L.CorticalAreas_dil_Colors.32k_fs_LR.label.gii L.sphere.32k_fs_LR.surf.gii fs_L-to-fs_LR.fsaverage.L_LR.spherical_std.164k_fs_LR.surf.gii BARYCENTRIC left.fsaverage164.label.gii` and `wb_command -label-resample Q1-Q6_RelatedParcellation210.R.CorticalAreas_dil_Colors.32k_fs_LR.label.gii R.sphere.32k_fs_LR.surf.gii fs_R-to-fs_LR.fsaverage.R_LR.spherical_std.164k_fs_LR.surf.gii BARYCENTRIC right.fsaverage164.label.gii`, 5) we then utilized the Freesurfer software to convert the label files to the Freesurfer annot files using the following commands: `mrconvert -annot left.fsaverage164.label.gii fs_L-to-fs_LR.fsaverage.L_LR.spherical_std.164k_fs_LR.surf.gii lh.HCP-MMP1.annot` and `mrconvert -annot right.fsaverage164.label.gii fs_R-to-fs_LR.fsaverage.R_LR.spherical_std.164k_fs_LR.surf.gii rh.HCP-MMP1.annot`, 6) we downloaded each individual subject’s Freesurfer pipeline derivative files from the HCP website and finally 7) we created volumetric files for each

individual for each parcellation using the Freesurfer command `mri_annotation2label` [57].

In addition, in order for performing parcellation matching with the ALE files, we did a similar process on the MNI152 brain.

This process allowed us to convert the parcellation data for HCP areas from the surface-based CIFTI file format to NIFTI-based volumetric coordinates. A single ROI was generated for each of the parcellations identified by the HCP to develop a cortical parcellation scheme [21].

2.3. ALE generation and identification of relevant cortical regions

We used BrainMap Ginger ALE 2.3.6 [58] to extract the relevant fMRI data for creation of an activation likelihood estimation (ALE). All coordinates were exported to Ginger ALE in the MNI coordinate space. We subsequently performed a Single Study analysis using Cluster-Level Interference (cluster level of 0.05, threshold permutations of 1000, uncorrected *p*-value of 0.001). The ALE coordinate data were displayed on an MNI-normalized template brain using the Multi-image Analysis GUI (Mango) 4.0.1 (ric.uthscsa.edu/mango). The pre-constructed ROIs of the parcellations were then overlaid on the ALE and compared visually for inclusion in the network.

2.4. Tractography

Working from the hypothesis that functionally connected regions of a network are likely structurally connected, we proceeded to determine the backbone of the network using deterministic tractography. All fiber tractography was done in DSI Studio (<http://dsi-studio.labsolver.org>) using publicly available brain imaging from the Human Connectome Project (<http://humanconnectome.org>, release Q3) [59,60]. Tractography was performed individually with 25 randomly chosen adult subjects. A multi-shell diffusion scheme was used, with *b*-values of 990, 1985, and 2980 s/mm². Each *b*-value was sampled in 90 directions. The in-plane resolution was 1.25 mm. The slice thickness was 1.25 mm. The diffusion data were reconstructed using generalized q-sampling imaging [59] The diffusion sampling length ratio was 1.25.

All reconstructions were performed in MNI space using a region of interest (ROI) approach to initiate fiber tracking from a seeded region. Greyordinate label parcellation fields were standardized to the three-dimensional volumetric working spaces of DSI studio using the structural imaging data provided by HCP for each subject. Voxels within each ROI were automatically traced with a maximum angular threshold of 45°. When a voxel was approached with no tract direction or a direction greater than 45°, the tract was halted. The number of fiber populations fit per voxel was 2. Tracts with length shorter than 30 mm or longer than 300 mm were discarded. In some instances, exclusion ROIs were placed to exclude spurious tracts or tracts inconsistently represented across individuals. Tracts were considered meaningful between parcellations if they could be identified consistently in five or more subjects.

3. Results

3.1. ALE regions and their corresponding parcellations

Fig. 1 demonstrates the ALE data of the 30 relevant fMRI experiments included in our meta-analysis, which included 311 healthy controls.

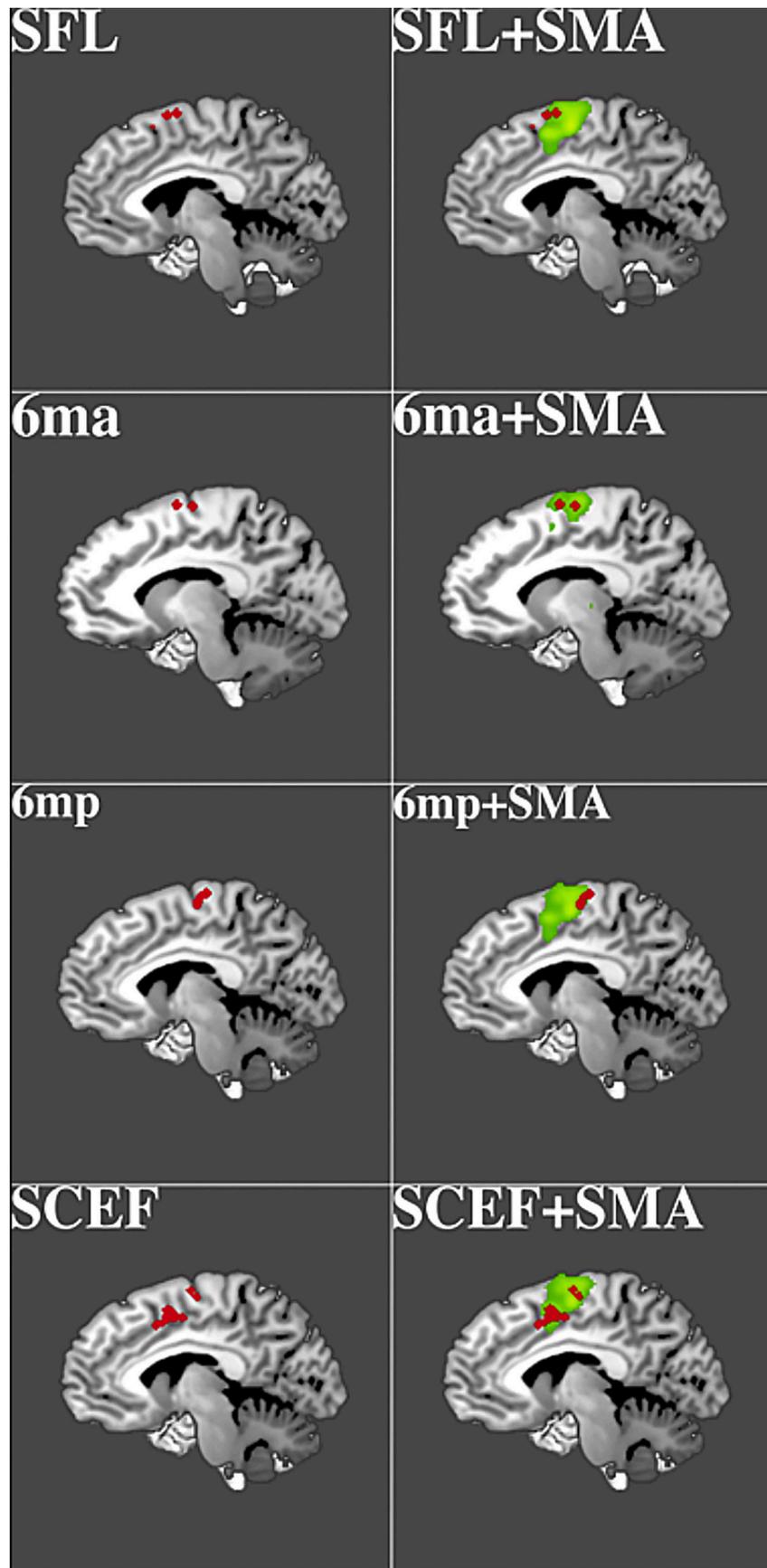


Fig. 2. Comparison overlay images between cortical parcellation and ALE data.

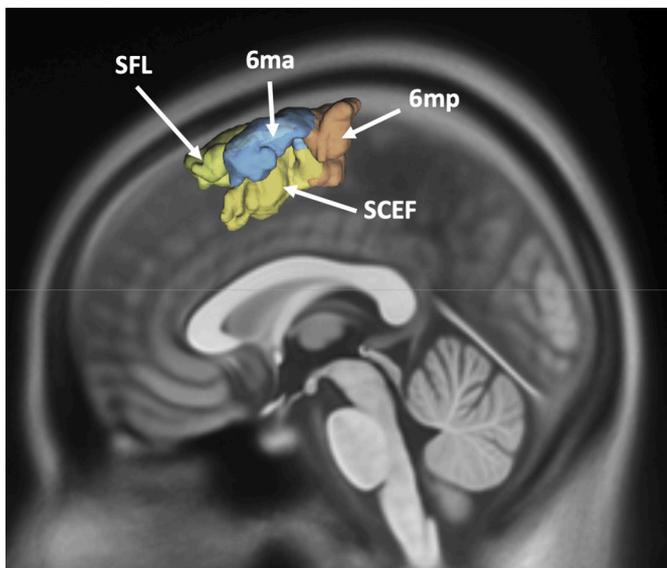


Fig. 3. Locations of brain parcellations involved in the SMA. SCEF: Supplementary and cingulate eye field, SFL: Superior frontal language area, 6mp: Brodmann area 6 medial parietal, 6ma: Brodmann area 6 medial anterior.

Highlighted areas are identified in the superior frontal gyrus immediately anterior to the central sulcus. Only regions in the left cerebral hemisphere were included in this analysis. Four parcellations overlap the ALE data in the region of the SMA. These include SFL, 6ma, 6mp, and SCEF, the names of these parcellations can be seen in Table 1. Comparison overlays between the cortical parcellation data and the ALE data are shown in Fig. 2. The ALE activated other brain regions in the Dorsal Premotor Area (4 and 6v). These were not included in the SMA model. Tasks involving the SMA would also activate these areas, and we chose to only use ALE data within the SMA region.

3.2. Structural connectivity of the supplementary motor area

Tractography was utilized to determine the connections from the SMA within and outside the motor system. These results are shown in Figs. 4 through 7, the varying colors are to demonstrate independence of

tracts and parcellations. ROIs showed consistent local connections between adjacent parcellations. All four parcellations comprising the SMA also had connections to the contralateral hemisphere and brainstem. In addition, we demonstrate the extra-motor connections of each parcellation. The connections found consistently across all 25 individuals included in our analysis are summarized in Fig. 3. A schematic showing the average number of tracts is shown in Fig. 8. The average strength of connection between parcellations can be seen in Table 2. (See Fig. 9.)

4. Discussion

In this study, we utilized meta-analytic software and deterministic tractography to construct an anatomical model of the supplementary motor area and its connections throughout the cerebral cortex. Our aim is to create a more specific anatomical map of the SMA for use in future studies. We found that areas SFL, 6ma, 6mp and SCEF were the cortical areas that comprise the SMA. While there are other possible ways to map this, we feel that it is critical that neuroimaging begin to move towards all of its data expressed in a single nomenclature which can be compared across studies, and a potential framework that we can build upon in future studies. Here we present an analysis of the parcellations included in our model and their cortical projections.

5. Ipsilateral connections

5.1. Primary motor cortex

Area 6mp of the SMA showed consistent connections to the primary motor cortex (Brodmann Area 4). Functionally, the SMA is known to connect to the primary motor area to facilitate numerous activities including speech, complex movement sets, and the mental rehearsing of movement [3,5–9,15,61].

5.2. Left inferior and middle frontal gyri

Areas SFL and 6ma show connections to ipsilateral left inferior frontal gyrus, specifically parcellations 44 and IFJa. The left inferior frontal gyrus has been shown to be involved in numerous aspects of verbal fluency and processing [62,63], characteristics also shared by functions of the SMA [7,9]. The left inferior frontal gyrus has also been implicated in other aspects of executive function including inhibition of

Table 2

Type and average strength of connection in SMA network.

	Left SFL	Left SCEF	Left 6mp	Left 6ma
Left SFL	0	144.40	51.76	64.96
Left SCEF	144.40	0	133.36	100
Left 6mp	51.76	133.36	0	64.48
Left 6ma	64.96	100	64.68	0
Left 8av	26.56	35.12	23.04	22.08
Left 44	8.08	24.64	23.92	35.12
Left 6d	3.36	14.32	9.84	7.12
Left 6a	98.72	196.48	134.48	134.0
Left 6r	12.48	28.88	24.72	48.0
Left 6v	14.0	32.32	29.12	25.36
Left FEF	4.48	10.96	4.64	3.92
Left 24dv	87.68	153.68	74.48	43.52
Left MI	9.36	14.56	7.04	9.36
Left FOP1	5.52	10.08	4.24	4.64
Left FOP3	12.80	18.64	5.28	9.68
Left FOP4	8.24	9.84	2.96	6.32
Left 7PL	0.25	0.25	0.08	0
Left MIP	0.75	1.0	0.92	0.58
Left 23c	13.12	32.16	37.68	10.32
Left 31 pv	5.76	17.44	15.12	3.20
Left V1	7.05	10.29	5.52	4.51

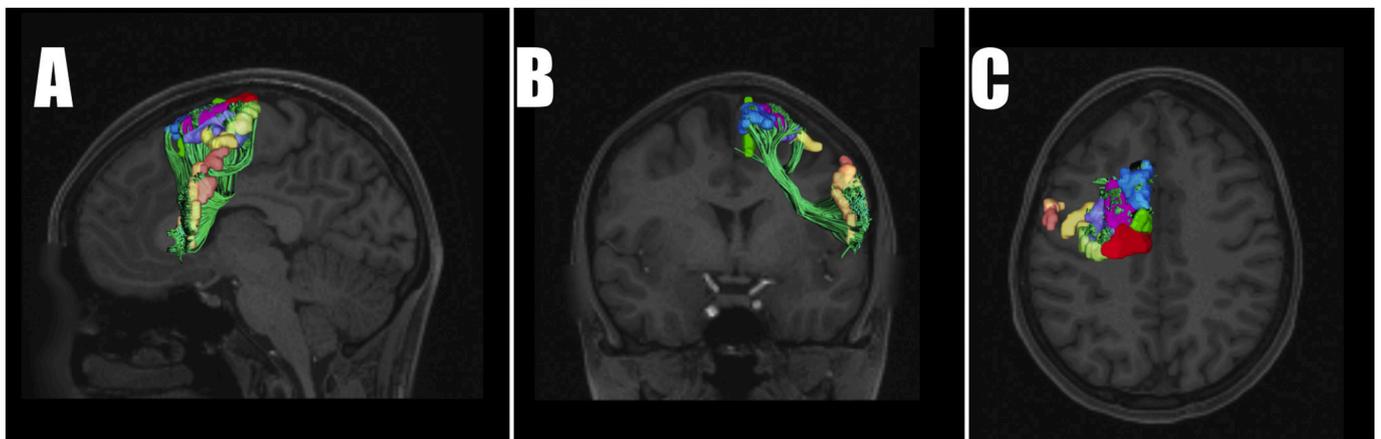


Fig. 4. Diffusion tractography showing all parcellations and basic model of the SMA.

inappropriate motor responses [50,64], a role that has also been linked to SMA function in recent studies [18,64–66]. Additionally, areas 6mp and 6ma of the SMA showed some connectivity to areas 46 and i6-8 of the middle frontal gyrus. This gyrus has also been implicated in aspects of overall executive function including action selection and action inhibition [67].

5.3. Anterior cingulate cortex

Area SCEF shows consistent connectivity to area p32pr of the anterior cingulate cortex (ACC). Functionally, the ACC has been linked to affect, action selection, and error detection [4,68]. This concept of action selection has also been attributed to the SMA, including aspects such as initiating internally cued movements [2–5,10].

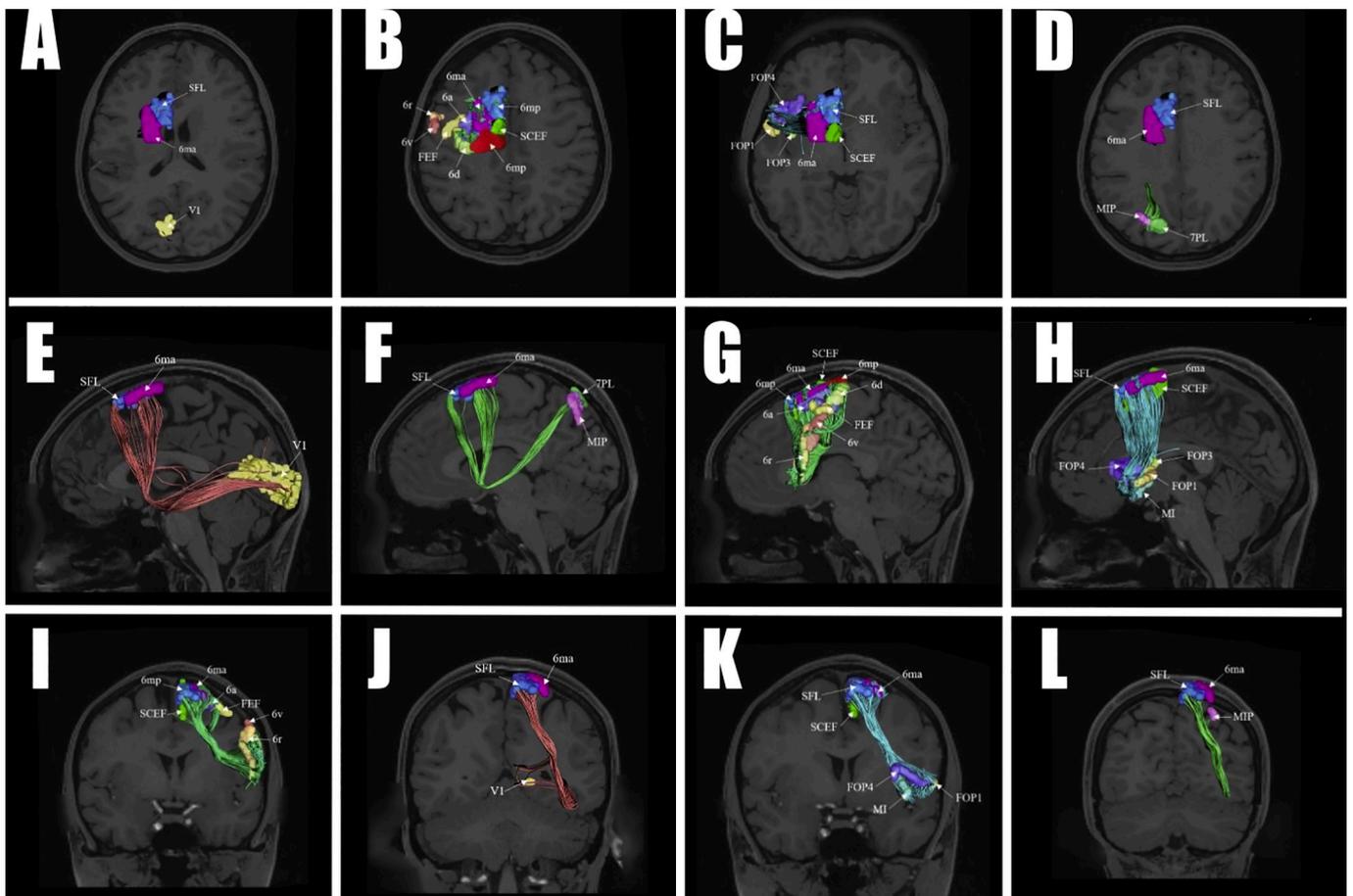


Fig. 5. Diffusion tractography showing connections of parcellations with 6ma.

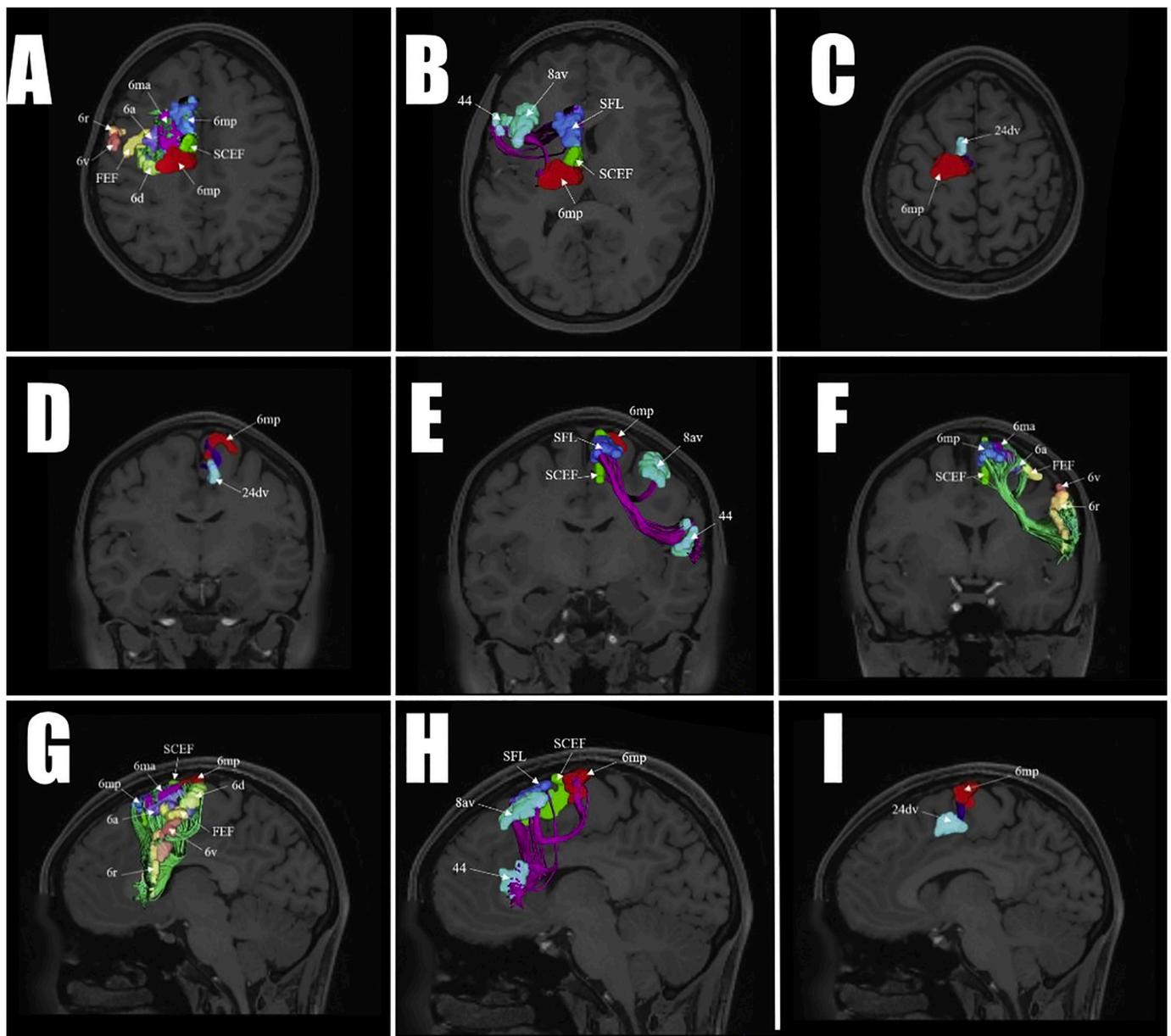


Fig. 6. Diffusion tractography showing connections of parcellations with 6mp.

5.4. Insula

The SMA shows strong connections to areas both within and near parcellations of the insula. These projections originate from SFL and 6ma and terminate in the ipsilateral insular areas MI and FOP4. These connections could explain the basis of insula-mediated motor responses to relevant environmental stimuli as well as proposed insula activity in the facilitation of speech production [61,69], two functions that have also been attributed to the SMA [9–12,65].

6. Contralateral connections

6.1. Supplementary motor area

The left SMA and each of its parcellations consistently showed connections to the contralateral supplementary motor area with tracts running through the corpus callosum. Such connections may explain the

role of the SMA in coordinating bimanual finger movement [16], and interhemispheric motor inhibitions [70,71]

6.2. Anterior cingulate cortex

Area SFL showed consistent connections to the contralateral area 8BM, a parcellation within the anterior cingulate. The ACC has been linked to affect, action selection and error detection [4,68]. It is possible that SMA activity in action selection and error detection are in part due to these connections to ipsilateral and contralateral anterior cingulate areas [2–5,10].

6.3. Lateral premotor cortex

Areas 6ma and SCEF both demonstrated consistent connections to the contralateral premotor parcellation 55b. Area 55b is a relatively understudied region of the human brain. It is believed that area 55b is

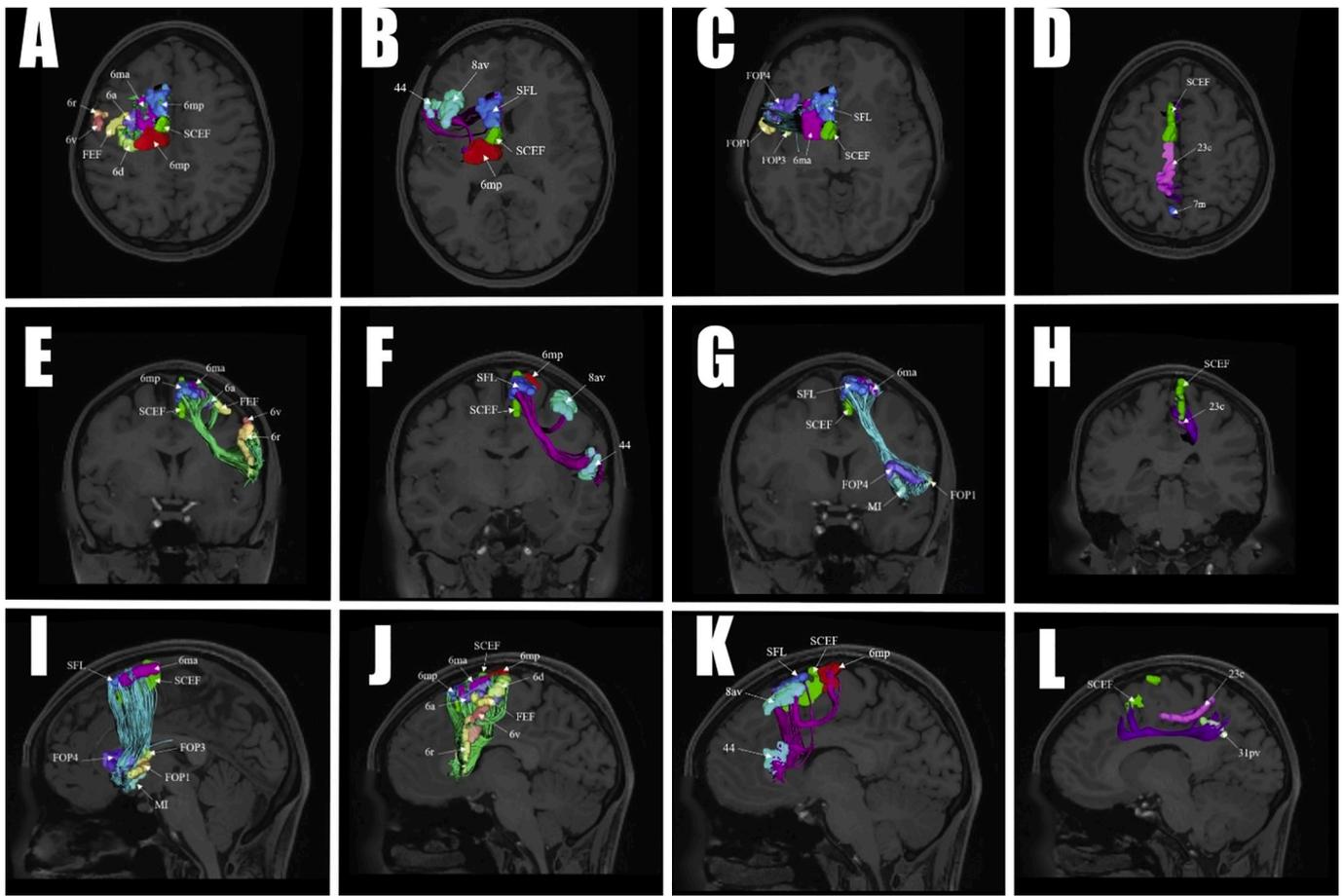


Fig. 7. Diffusion tractography showing connections of parcellations with SCEF.

involved in the processing of language [72], likely integrating information from the SMA to initiate speech [7–9]. Recently, 55b was demonstrated to be part of the negative motor area of the face and upper limb [73].

6.4. Right inferior frontal gyrus

In considering connections that were found to be less consistent across individuals, areas SCEF and 6ma showed some connections to the contralateral inferior frontal gyrus parcellations 8C and IFJp. The right inferior frontal gyrus is activated when important stimuli are detected. This activation can lead to complex motor inhibiting and activating responses [74,75]. Both response inhibition and activation based on external cues have been linked to SMA activity [10–13,18,64–66,76].

7. SMA as a motor planning area

It has been found that parcellations surrounding the SMA are a part of diverse networks [77,78]. As a result, we may need to rework what we mean by motor planning areas. Motor planning areas involve combinations of areas that correlate strongly with other networks, such as the Default Mode Network and Salience Network [77,78]. This indicates the SMA may have a more diverse cognitive repertoire than merely as a planning motor area. Further, a study that mapped the functional cortical networks to HCP parcellations demonstrated that motor planning areas are functionally a part of different networks [78]. Together, this argues that motor planning is a combination of control networks and motor at their junction and highlights motor planning is a more

complicated task than purely motor.

8. Limitations

Meta-analyses using ALE data has some limitations. The data we produced in this research is limited by the quality of the evidence that was available to be included in our analyses. For that reason, by describing the connections of the SMA in the HCP parcellation scheme, future work using machine-learning can validate and elucidate these findings further. As described by the HCP, they have identified their parcellation scheme based on areal boundaries when they were strongly supported by multiple modalities [21]. There is, however, the possibility that the scheme is incomplete, or there may be finer grained parcellations [21]. We believe, that describing the SMA in terms of this nomenclature is a beneficial first step towards understanding the structure and function of the SMA in more detail as it allows for direct cross-study comparisons. Additionally, traditional cross-subject volume-based studies, which were included in our analyses, may degrade cortical area localization and alignment when compared to surface-based approaches, such as the HCP processing [79]. Individual subject HCP pipelines may provide different results, however it is difficult to examine this in the literature [79].

It's important to note that there are some challenges of quantifying area to area diffusion tractography. While studies using monkey tracing tractography show a rough correlation, it's hard to be certain about the terminus of these tracts. It's important to note that the data coming out of the present study is relative rather than obsolete as there's difficulty in defining boundaries. For example, Donahue et al., note that diffusion

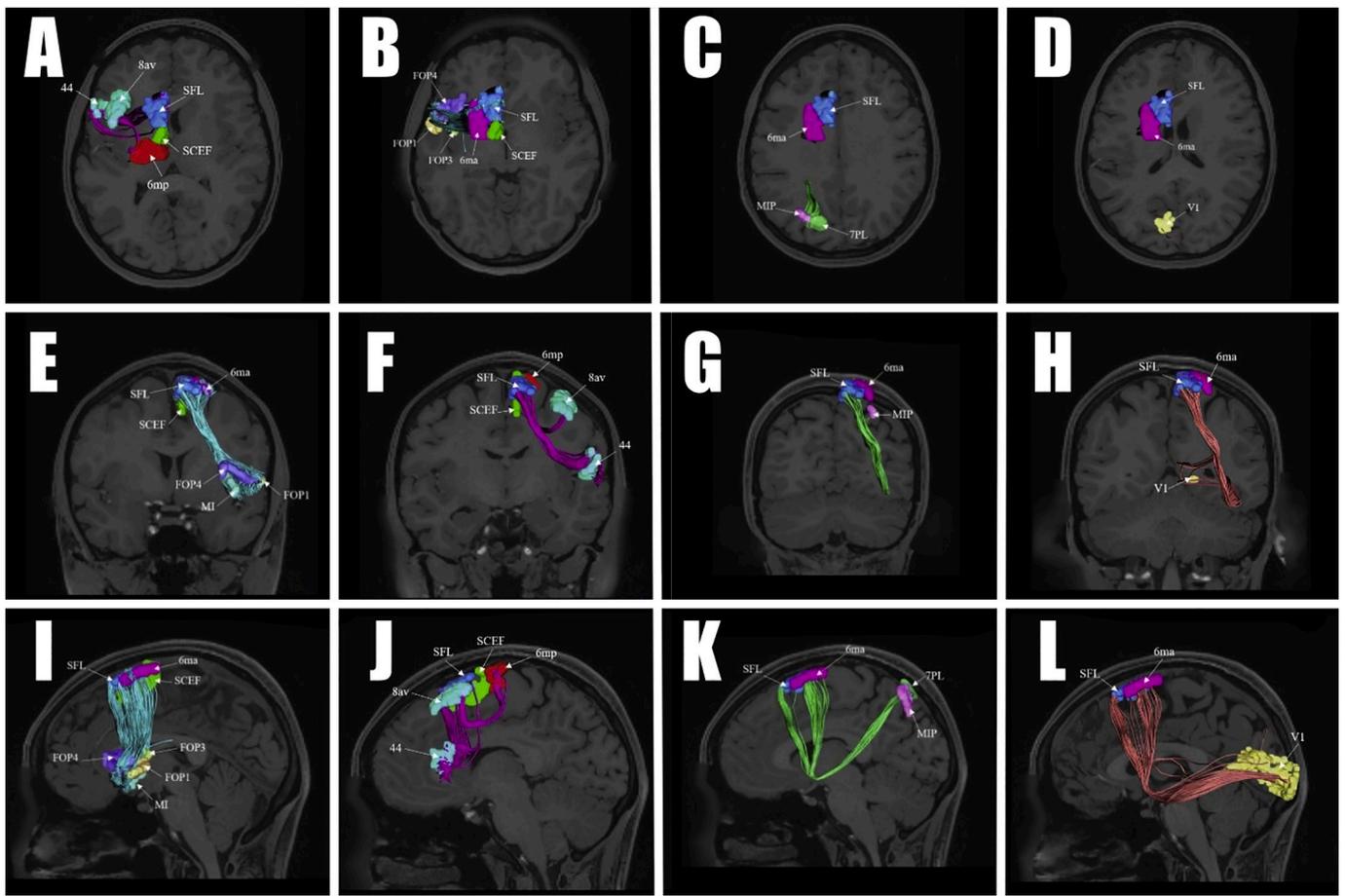


Fig. 8. Diffusion tractography showing connections of parcellations with SFL.

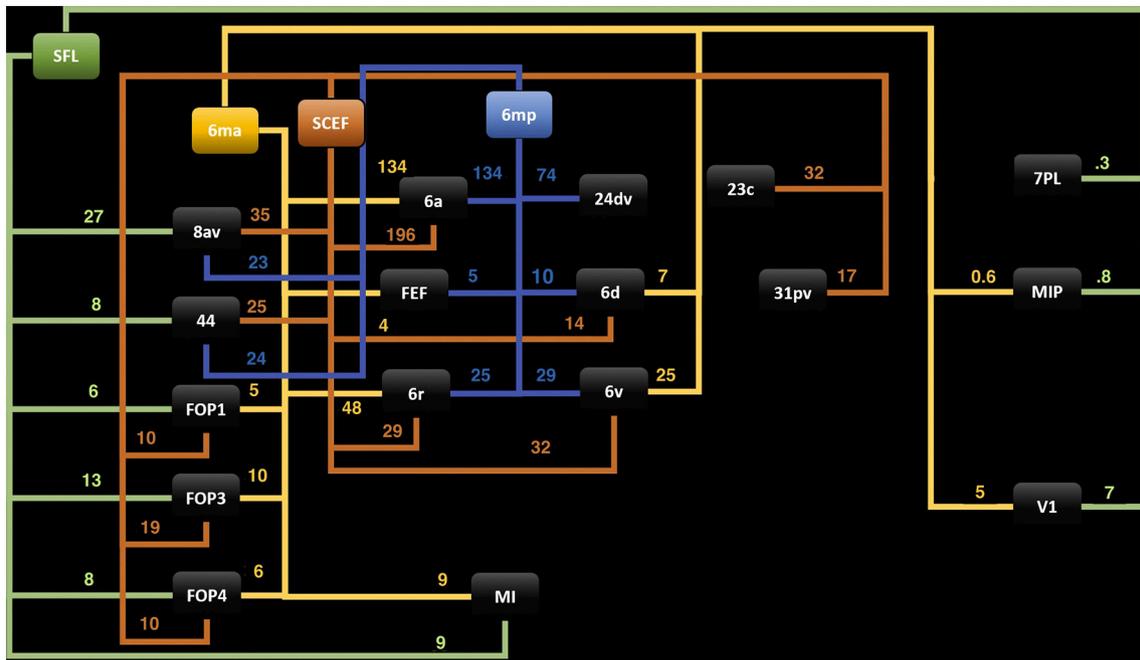


Fig. 9. A wire schematic of the connections found in the study. The numbers indicate the average number of tracts between two areas.

tractography in monkeys is a fair detector of cortical tracts and reasonably good predictor for the strength of connection [80]. Additionally, they state the HCP data used in this study could produce comparable results, however, given anatomical and methodological diversity, the quality of the provided evidence may be limited to within one or two orders of magnitude compared to ground truth [80].

9. Conclusions

We present a preliminary anatomical model of the SMA and its connections within and without the motor system. Further studies may refine this model with the ultimate goal of clinical application in neurosurgical planning, transcranial magnetic stimulation treatment and/or to understand large-scale datasets.

Disclosures

Dr. Michael Sughrue is the Chief Medical Officer of Omniscent Neurotechnology. No products relating to this were discussed in this paper. The other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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