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Parcellation-based modeling of the dorsal premotor area

John R. Sheets[a], Robert G. Briggs[a], Michael Y. Bai[b], Anujan Poologaindran[c], Isabella M. Young[d], Andrew K. Conner[a], Cordell M. Baker[a], Chad A. Glenn[a], Michael E. Sughrue[b,*]

[a] Department of Neurosurgery, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States of America
[b] Centre for Minimally Invasive Neurosurgery, Prince of Wales Private Hospital, Sydney, Australia
[c] Brain Mapping Unit, University of Cambridge, Cambridge, UK
[d] Cingulum Health, Sydney, Australia

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ABSTRACT

Background: The dorsal premotor area (DPM) plays an important role in hand coordination and muscle recruitment for lifting activities. Lesions in the area have demonstrated that the DPM is critical in the integration of movements that require combinations of reaching, grasping, and lifting. While many have looked at its functional connectivity, few studies have shown the full anatomical connectivity of DPM including its connections beyond the motor network. Using region-based fMRI studies, we built a neuroanatomical model to account for these extra-motor connections.

Objective: In this study, we performed meta-analysis and tractography with the goal of creating a map of the dorsal premotor network using the Human Connectome Project parcellation scheme nomenclature (i.e. the Glasser Atlas). 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.

Methods: Thirty region-based fMRI studies were used to generate an activation likelihood estimation (ALE) using BrainMap software (Research Imaging Institute of Texas Health Science Center San Antonio). Cortical parcellations overlapping the ALE were used to construct a preliminary model of the Dorsal Premotor Area. Diffusion spectrum imaging (DSI) based tractography was performed to determine the connectivity between cortical parcellations and connections throughout cortex. The resulting connectivities were described using the cortical parcellation scheme developed by the Human Connectome Project (HCP).

Results: Three left hemisphere regions were found to comprise the Dorsal Premotor Area. These included areas 6a, 6d. and 6v, Across mapped brains, these areas showed consistent interconnections between each other. Additionally, ipsilateral connections to the premotor cortex, sensorimotor cortex, superior and inferior parietal lobule, middle and inferior frontal gyrus, and insula were demonstrated. Connections to the contralateral supplementary motor area and premotor cortex were also identified.

Conclusions: We describe a preliminary cortical model for the underlying structural connectivity of the Dorsal Premotor Area. Future studies should further characterize the neuroanatomic underpinnings of this network.

1. Introduction

The dorsal premotor area (DPM) is a critical component of the motor network. It is known to aid in the coordination of reaching and grasping actions, complex hand movements, and muscle recruitment during lifting [1–10]. Lesions to the DPM explain its particular role in the integration of grasping and lifting movements [2,3,7]. The DPM has also been shown to be active in the learning of sequence-specific visuomotor sequences [11,12], and more recently, the DPM has been functionally linked to auditory-motor integration and response [13–16].

While the functional significance of the DPM is well established, the underlying structural connectivity of this part of the cerebral cortex has not been described in any great detail. To date, there are few studies that detail the anatomical map of the DPM with its complete cortical connection patterns. Identifying and describing the extra-motor connections between the DPM and other parts of the cerebral cortex is of particular interest as such connections may explain how the motor

* Corresponding author at: Centre for Minimally Invasive Neurosurgery, Suite 3, Level 7 Barker St, Prince of Wales Private Hospital, Randwick NSW 2031, Australia.
E-mail address: sughruevs@gmail.com (M.E. Sughrue).

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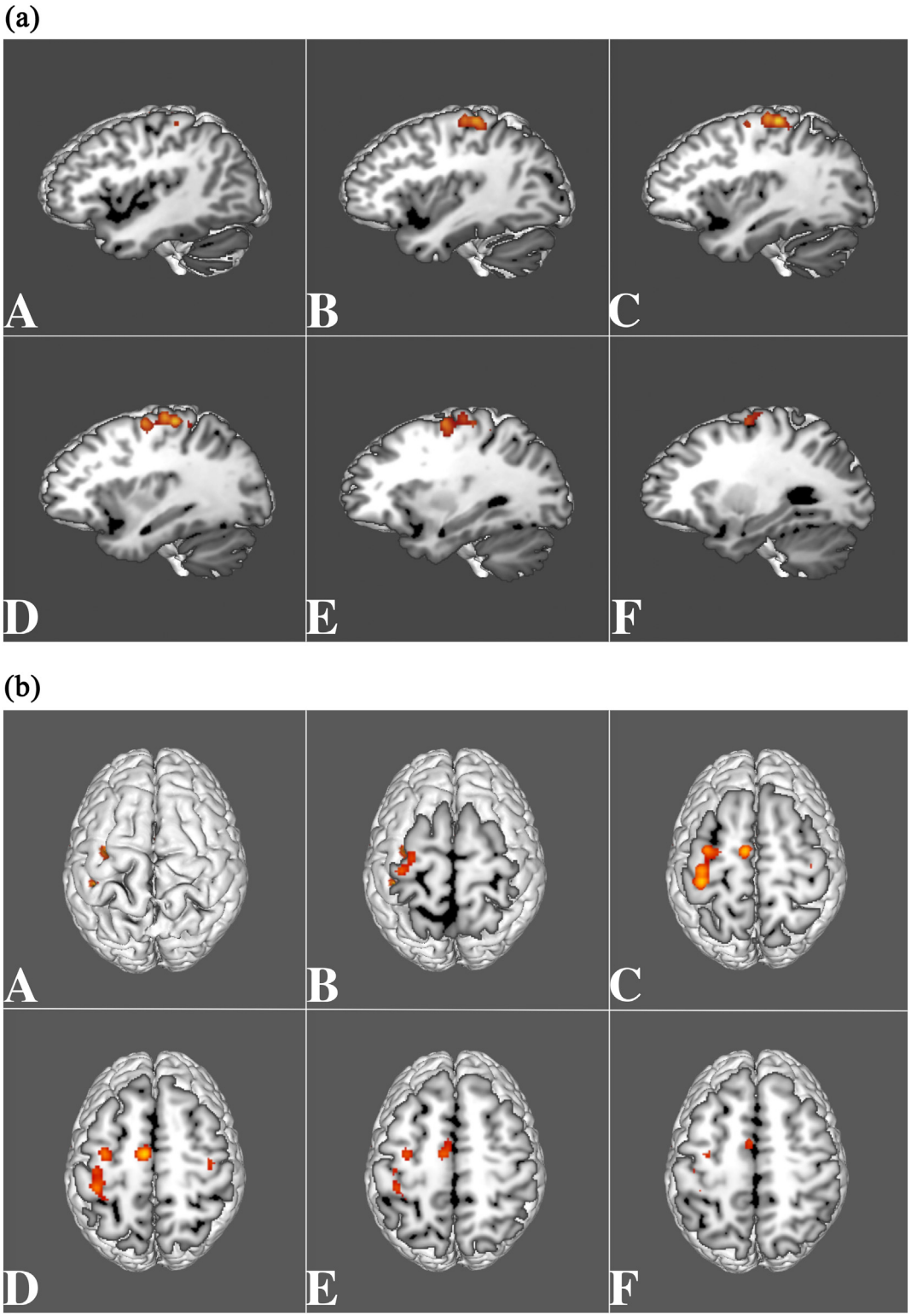

Fig. 1a. Representative sagittal images on a sample MNI brain showing the generated ALE of the DPM.

network modulates cerebral activity beyond motor function.

In this study, we constructed a model of the DPM based on the cortical parcellation scheme published from the Human Connectome Project (HCP) [17]. Using relevant task-based functional magnetic resonance imaging (fMRI) studies and BrainMap (Research Imaging Institute of Texas Health Science Center San Antonio), a collection of open-access software programs used to generate activation likelihood estimations (ALE) from fMRI studies, we identified the key cortical areas involved in the DPM. After identifying these regions of interest, we performed diffusion spectrum imaging (DSI) based fiber tractography to determine the structural connectivity between parcellations, both within and beyond the motor network. Our goal is to provide a more detailed anatomic model of the DPM and its extra-motor connections for use in future studies.

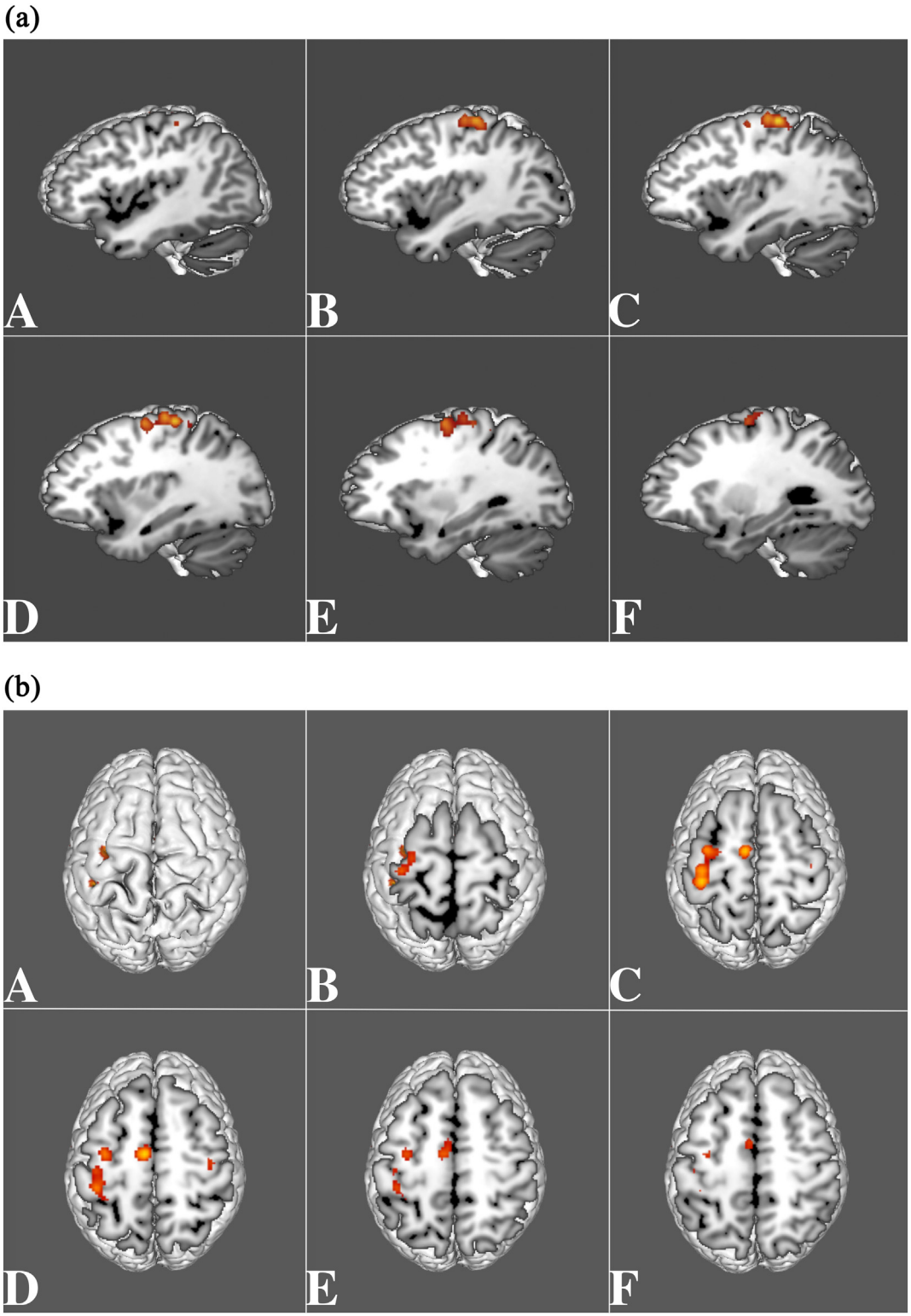

Fig. 1b. Representative axial images on a sample MNI brain showing the generated ALE of the DPM.

2. Methods

2.1. Literature search

We utilized BrainMap Sleuth 2.4 (Research Imaging Institute of Texas Health Science Center San Antonio) on July 20, 2017 to search for all relevant task-based fMRI studies related to the dorsal premotor area [18–20]. We used the keyword search algorithm for terms related to the dorsal premotor cortex or premotor cortex, or for studies related to motor function (behavioral domain is related to action execution or imagination or response type is related to motor activity, such as finger tapping or flexion/extension) to identify all studies connecting DPM motor activity to other parts of the cortex. Studies were included in our analysis if they met the following criteria: (1) peer-reviewed publication, (2) task-based fMRI study related to the DPM cortex, (3) based on whole-brain, voxel-wise imaging, (4) including standardized

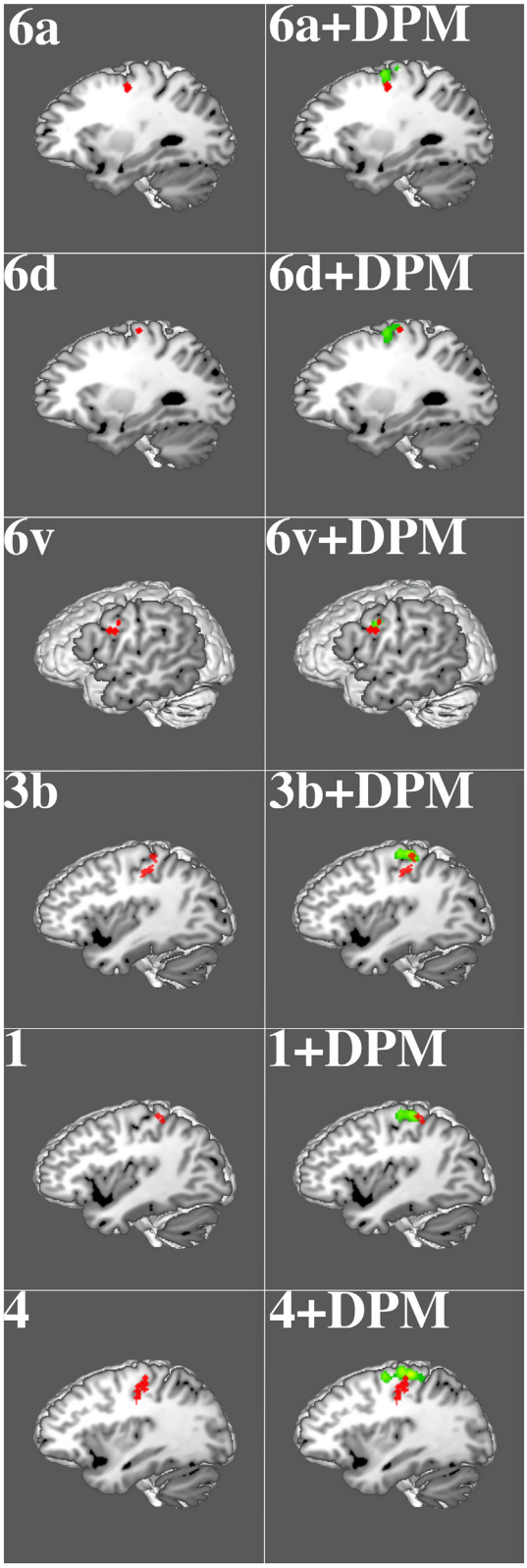

Fig. 2. Comparison overlay images between cortical parcellation and ALE data. (Panel 1): with 6a, (Panel 2): with 6d, (Panel 3): with 6v, (Panel 4): with 3b, (Panel 5): with 1, (Panel 6): with 4.

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 analysis. Overall, 30 papers related to the DPM met criteria for inclusion in this study [21–50].

2.2. Creation of 3D regions of interest

The three-dimensional regions of interest (ROIs) used in this study were generated from data previously published by the HCP authors [17]. In their study, the authors used surface-based greyordinates to study 180 cortical ROIs. Greyordinate data were converted to volumetric dimensions using the Connectome Workbench command line interface (Van Essen Laboratory, Washington University 2016). A single ROI was generated for each of the parcellations identified by the HCP authors [17].

2.3. ALE generation and identification of relevant cortical regions

The activation coordinates cited within each experiment from the literature search were exported in MNI space from BrainMap Sleuth 2.4 to use in BrainMap GingerALE 2.3.6 (Research Imaging Institute of Texas Health Science Center San Antonio). GingerALE utilizes the MNI co-ordinates and the corresponding studies' sample size to create an activation likelihood estimation (ALE) [51–53]. An ALE models the likely convergence of foci based on MNI coordinates and is commonly used in meta-analyses of fMRI data to demonstrate areas of activity that are associated with a task or brain network, in this case it is to determine the network of the DPM [51]. The ALE was created using a single study analysis with 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. Tasks which activate the DPM will also generally activate the motor cortex, thus areas that form a part of the primary motor cortex were excluded from the model of the DPM.

2.4. 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) [54,55],. Tractography was performed individually with 10 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 [56]. 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 [57]. Grey ordinate 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 [58]. Voxels within each ROI were automatically traced with a maximum angular threshold of 45 degrees. When a voxel was approached with no tract direction or a direction greater than 45 degrees, the tract was halted. Tracks 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. 1a and 1b demonstrates the ALE of the 30 relevant fMRI studies

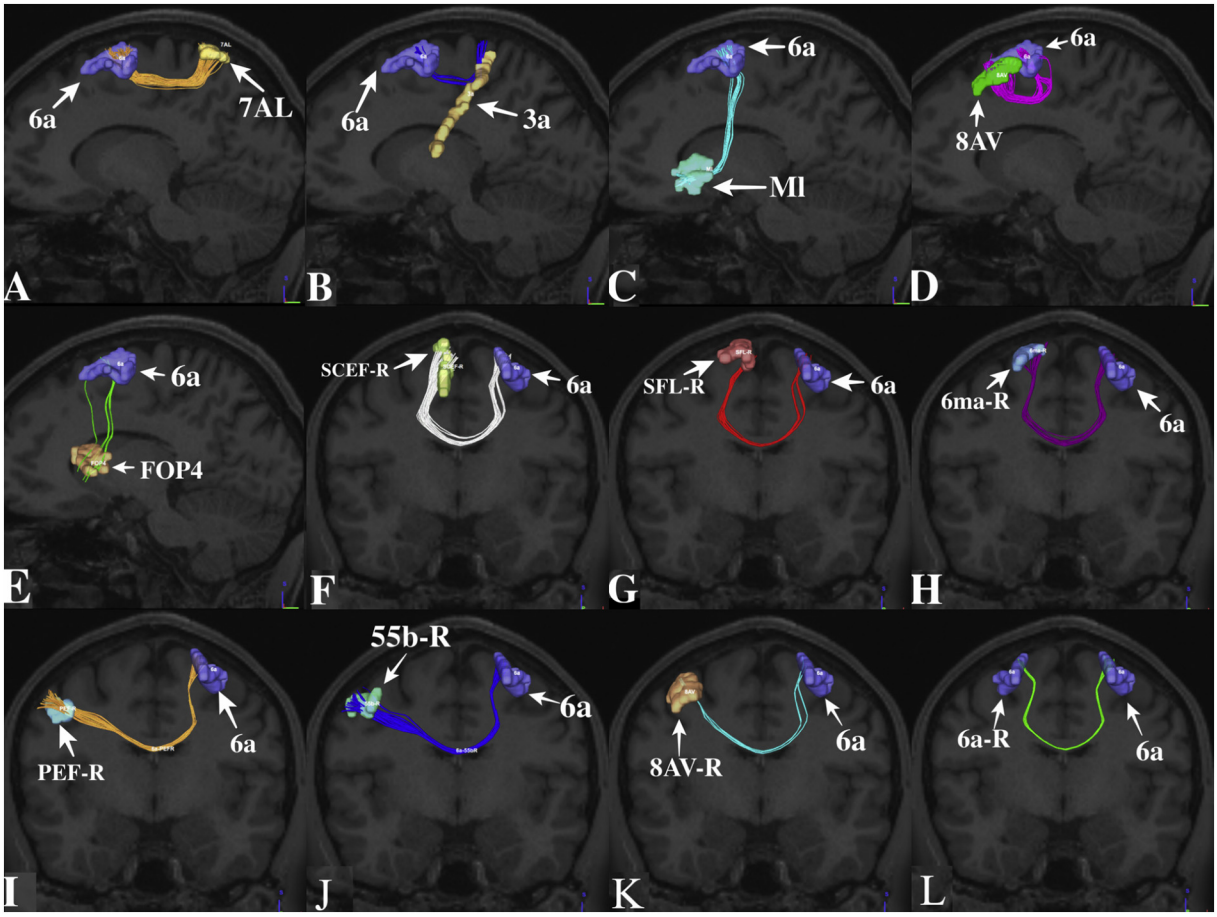

Fig. 3. Diffusion tractography showing connections of parcellations with 6a. (A): with 7AL, (B): with 3 ac, (C): with MI, (D): with 8AV, (E): with FOP4, (F): with SCEF-R, (G): with SFL-R, (H): with 6ma-R, (I): with PFE-R, (J): with 55b-R, (K): with 8AV-R, (L): with 6a-R.

included in our meta-analysis. The highlighted regions in Fig. 1a and 1b correspond to the ALE of the DPM and are identified in the precentral and postcentral gyri. For simplicity, only regions in the left cerebral hemisphere were included in this analysis. Three parcellations were found to overlap the ALE data in the region of the DPM: 6a, 6d, and 6v. Areas 3b, 1 and 4 also overlapped the ALE data, however they were excluded from our model of the DPM as they are regions of the Primary Motor Area. Comparison overlays between the cortical parcellation data and the ALE data are shown in Fig. 2.

3.2. Structural connectivity of the dorsal premotor area

Tractography was utilized to determine the underlying structural connections of the DPM outside the motor network. ROIs showed consistent local connections between adjacent parcellations. Both ipsilateral and contralateral connections are shown for each individual parcellation with an additional overlay including all DPM connections to the brainstem and a full overlay of all DPM projections throughout the cerebral cortex. The connections found consistently across all 25 subjects included in our analysis are summarized in Figs. 3 through 5. A summary map is shown in Fig. 6. A schematic showing the average number of tracts is shown in Fig. 7. Table showing all average numbers is shown in Table 1.

4. Discussion

In this study, we performed meta-analysis and tractography with the goal of creating a map of the dorsal premotor network using the Human Connectome Project parcellation scheme nomenclature (i.e. the Glasser Atlas). While there are other possible ways to map this, such as intraoperative mapping, this paper aims to provide a foundational anatomic work to support future exploratory work. 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.

4.1. Connections to the premotor cortex

The DPM and its associated parcellations show extensive connections with many other premotor parcellations not considered part of DPM. Area 6d has connections with premotor area 6a. Additionally, area 6a showed contralateral connections to premotor areas 55b-R, 6a-R, and PEF-R, and area 6d showed contralateral connections to premotor areas PEF-R and 55b-R. While it could seem obvious that the dorsal premotor area as described in this paper has connections to many other areas classically associated with a “premotor” function, these connections could explain some of the functional specificity associated with DPM exclusively. The premotor cortex has long been associated with its ability to facilitate movement [8] but additionally, and more specifically, these connections outside of DPM to additional premotor areas could explain the DPM activation seen in activities such as visual attention, via FEF, and language-related activities, areas 55b and 6r [59–61]. Specifically, connections to these language-related areas could explain some the newly suggested functions of DPM such as auditory-motor integration and response. Finally, it was recently demonstrated that a distinct sub-region within the left DPM area supported abstract cognitive functions [62].

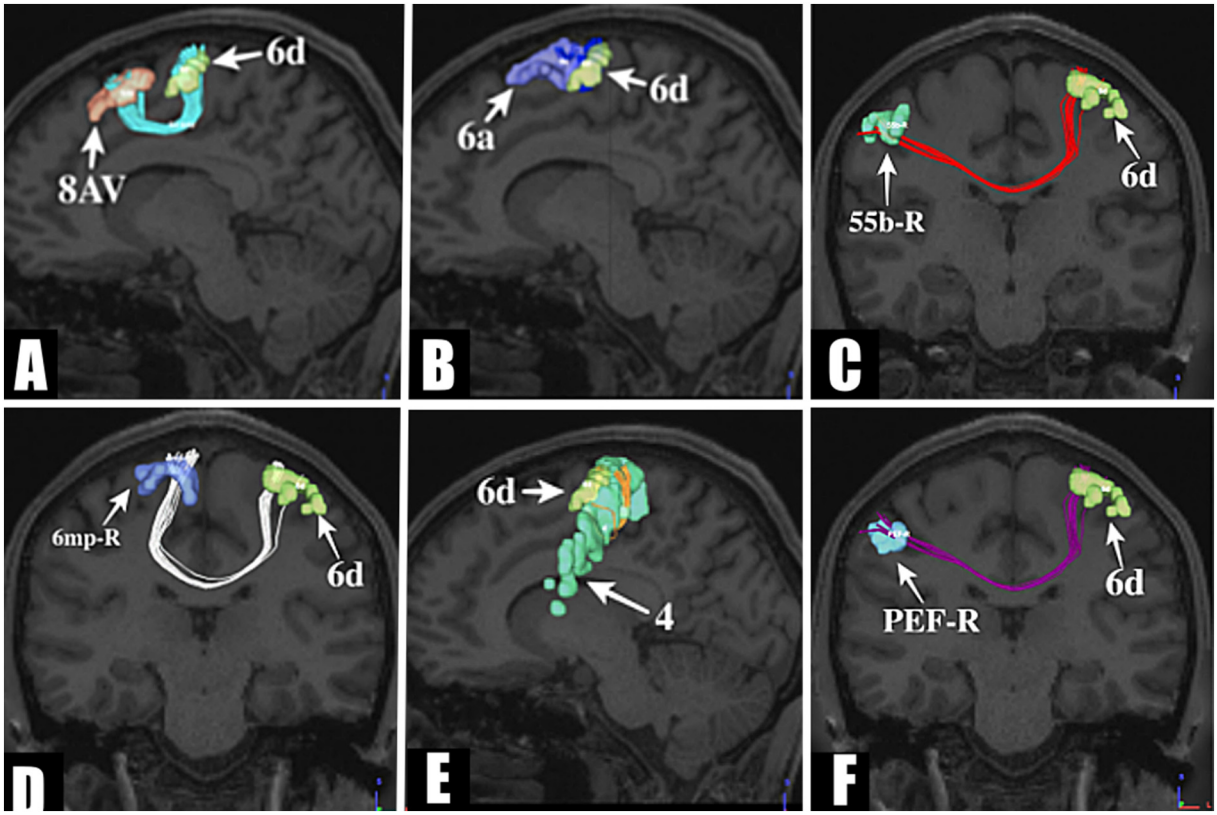

Fig. 4. Diffusion tractography showing connections of parcellations with 6d. (A): with 8AV, (B): with 6a, (C): with MI55b-R, (D): with 6mp-R, (E): with 4, (F): with PFE-R.

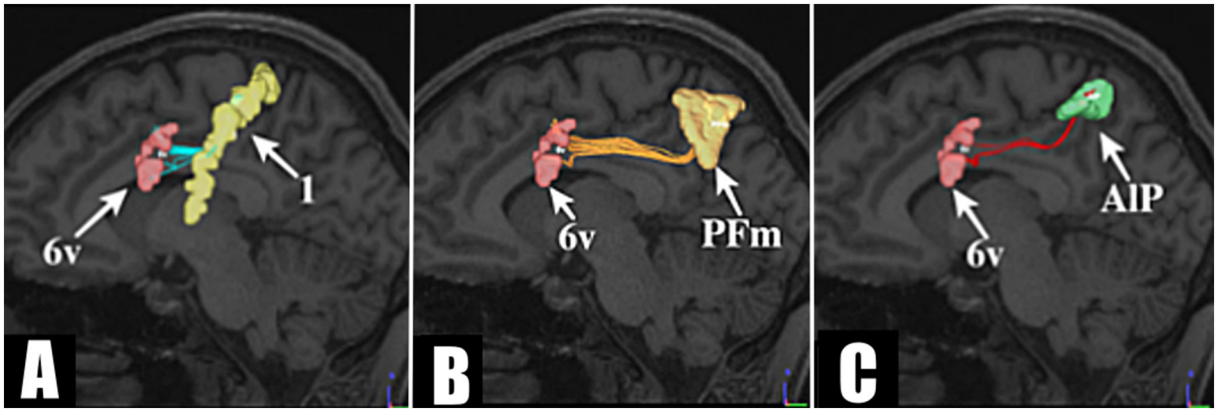

Fig. 5. Diffusion tractography showing connections of parcellations with 6v. (A): with 1, (B): with PFm, (C): with AIP.

4.2. Connections to the supplementary motor area

Area 6a showed connections to contralateral areas deemed to be a part of the Supplementary Motor Area (SMA) including SCEF-R, SFL-R, and 6ma-R. Additionally, area 6d of the DPM showed connections to contralateral SMA area 6mp-R. SMA has been shown to be involved in a variety of both internally and externally cued tasks including reaching, grasping, and speech [63–67]. These are functions that have also been attributed to regions located within DPM, and these white matter connections could serve as an explanation of function.

4.3. Connections to the sensorimotor cortex

Areas 6a of the DPM showed connections to area 3a of the sensorimotor cortex. Area 3a is known to receive information regarding information from deep body tissues [68]. This type of sensation is especially important in a chronic pain setting [69]. Additionally, area 3a is known to be involved in proprioceptive sensation [69]. In terms of proprioception especially, a functional relationship can be clearly observed between the areas of DPM and 3a. Proprioception is a critical aspect to many of the complex hand movements and reaching/grasping actions generated by DPM. This anatomical connection to an area of proprioception could explain what allows DPM to coordinate such movements.

4.4. Connections to the inferior and superior parietal lobules

Area 6v of DPM showed connections to IPL area PFm. IPL has been implicated in spatial perception and also integration of visuomotor tasks [70]. The ability to perceive distance and integrate visual cues

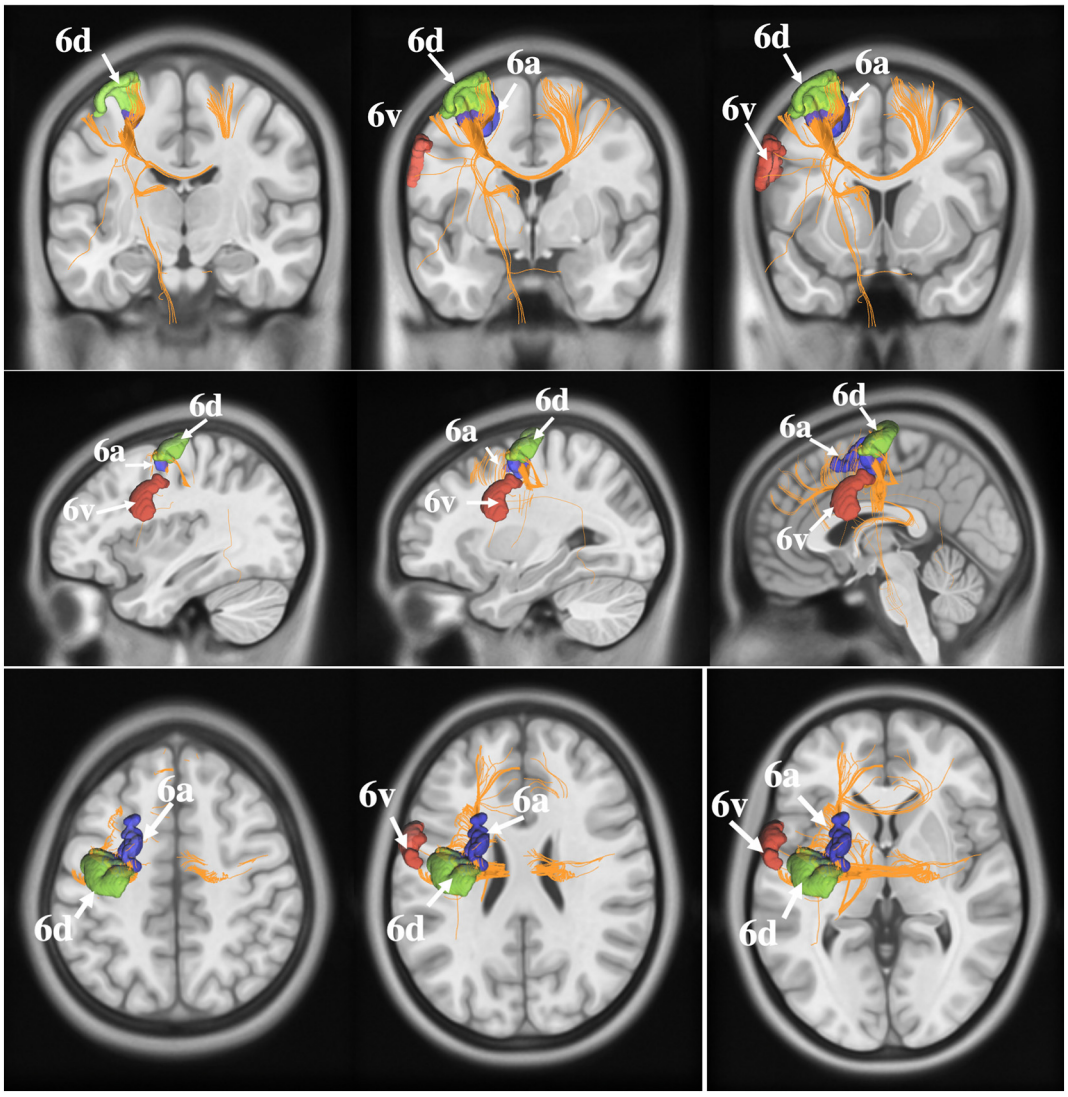

Fig. 6. Diffusion tractography showing all parcellations and basic model of the DPM: 6a, 6d and 6v in coronal, sagittal and axial planes.

into motor tasks would seem to be a critical aspect of many of the functions associated with DPM activity. Such reaching/grasping, lifting, and complex hand movements could not be achieved without a significant amount of perceptive ability and visuomotor integration, likely provided by area IPL. Additionally, area 6v of the DPM showed connections to area AIP of the Superior Parietal Lobule (SPL). Area 6a of the DPM also showed connections to 7AL of the SPL. Regions of the SPL have been suggested to function in visually-guided motor tasks and also in creating an internal representation of one's whole body in space, two functions critical to many of the roles associated with DPM activity [71]. Moreover, it was recently demonstrated that the SPL and DPM differ significantly in hand trajectory planning: the former was recruited only during simple and straight hand trajectories, but the latter is recruited during computationally-intensive and complex reach planning [62].

4.5. Connections to the left middle and inferior frontal gyrus

Areas 6a and 6d of DPM showed connections to area 8AV of the Middle Frontal Gyrus (MFG). The Left MFG has been implicated in aspects of executive function including action selection, action inhibition, and verbal fluency/processing [72–75]. These aspects of executive function are especially important to many of the roles attributed to DPM, and these functional connections that were observed could serve to explain DPM functionality.

4.6. Connections to the insula

Area 6a of DPM showed connections to Insula areas MI and FOP4. The insula is proposed to be involved in coordinating motor responses to relevant environmental stimuli [76]. These responses could be automatic in nature and anatomical connections of DPM to Insula could explain some of the functions that have been attributed to DPM areas. Specifically, DPM is known to play a role in visuomotor sequence learning and auditory-motor integration [11–16]. Insular connections could attribute to reflexive responses of this nature.

5. Conclusions

We present a preliminary anatomic model of the dorsal premotor area and its connections within and beyond the motor system. Further studies may refine this model with the ultimate goal of clinical application.

Compliance with ethical standards

All research was conducted to the highest ethical standards. No aspect of this study involved human participants or animals, and so

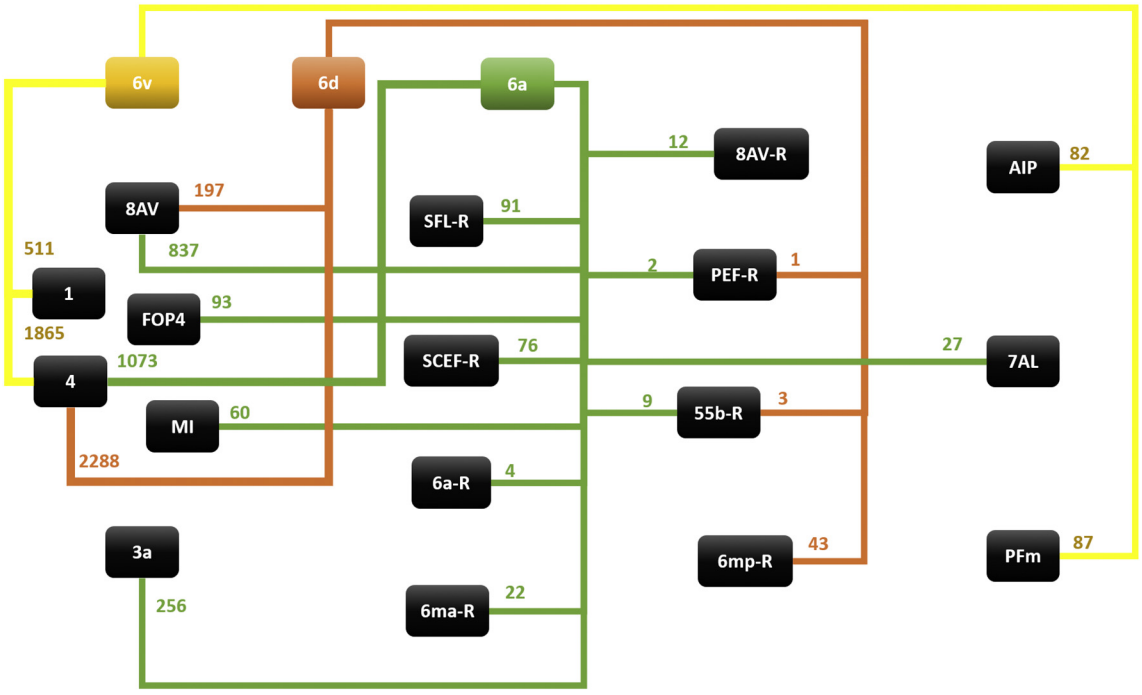

Fig. 7. A wire schematic of the connections found in the study. The numbers indicate the average number of tracts between two areas.

Table 1
Type and average strength of connection (± standard error) in the DPM network.

	Left_6d	Left_6v	Left_6a
Left_6d	–	92.40 (± 57.63)	1897.92 (± 355.78)
Left_6v	92.4 (± 57.63)	–	91.20 (± 44.71)
Left_6a	1897.92 (± 355.78)	91.20 (± 44.71)	–
Left_3a	770.32 (± 122.66)	324.56 (± 124.94)	255.2 (± 81.85)
Left_7AL	61.20 (± 38.16)	14.4 (± 13.50)	26.56 (± 15.49)
Left_8Av	194.00 (± 94.15)	176.56 (± 53.37)	839.68 (± 214.90)
Left_FOP4	45.68 (± 36.71)	136.08 (± 101.94)	92 (± 57.18)
Left_MI	62.32 (± 29.83)	89.92 (± 78.09	60.48 (± 29.15)
Left_AIP	100.48 (± 47.60)	80.24 (± 50.00)	99.52 (± 44.29)
Left_PFm	54.24 (± 42.68)	83.36 (± 65.34)	75.04 (± 38.99)
Right_PEF	1.36 (± 1.36)	2.64 (± 1.96)	1.84 (± 1.85)
Right_55b	3.12 (± 3.04)	5.92 (± 4.67)	9.20 (± 5.65)
Right_SFL	39.52 (± 38.03)	22.08 (± 19.31)	91.20 (± 67.09)
Right_SCEF	47.52 (± 36.81)	24.64 (± 19.45)	77.04 (± 51.85)
Right_6ma	13.12 (± 12.79)	11.52 (± 10.87)	21.68 (± 20.44)
Right_6mp	43.2 (± 18.56)	11.04 (± 8.44)	30.08 (± 16.10)
Right_8Av	8.16 (± 8.16)	10.16 (± 9.99)	11.84 (± 11.43)
Right_6a	3.04 (± 2.35)	7.04 (± 3.43)	4.32 (± 3.92)

informed consent was not required. Institutional review board approval was not required to conduct this study.

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