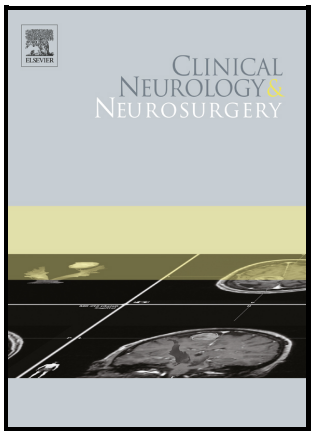

A Connectivity Model of the Anatomic Substrates Underlying Ideomotor Apraxia: A Meta-Analysis of Functional Neuroimaging StudiesRunning Title: Model of the Ideomotor Apraxia Network

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A Connectivity Model of the Anatomic Substrates Underlying Ideomotor Apraxia: A Meta-Analysis of Functional Neuroimaging Studies

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Running Title: Model of the Ideomotor Apraxia Network

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ABSTRACT

Background: Patients with ideomotor apraxia (IMA) present with selective impairments in higher-order motor cognition and execution without damage to any motor or sensory pathways. Although extensive research has been conducted to determine the regions of interest (ROIs) underlying these unique impairments, previous models are heterogeneous and may be further clarified based on their structural connectivity, which has been far less described.

Objective: The goal of this research is to propose an anatomically concise network model for the neurophysiologic basis of IMA, specific to the voluntary pantomime, imitation and tool execution, based on intrinsic white matter connectivity.

Methods: We utilized meta-analytic software to identify relevant ROIs to ideomotor apraxia reported in the literature based on functional neuroimaging data with healthy participants. After generating an activation likelihood estimation (ALE) of relevant ROIs, cortical parcellations overlapping the ALE were used to construct an anatomically precise model of anatomic substrates using the parcellation scheme outlined by the Human Connectome Project (HCP). Deterministic tractography was then performed on 25 randomly selected, healthy HCP subjects to determine the structural connectivity underlying the identified ROIs.

Results: 10 task-based fMRI studies met our inclusion criteria and the ALE analysis demonstrated 6 ROIs to constitute the IMA network: SCEF, FOP4, MIP, AIP, 7AL, and 7PC. These parcellations represent a fronto-parietal network consisting mainly of intra-parietal, U-shaped association fibers (40%) and long-range inferior fronto-occipital fascicle (IFOF) fibers (50%). These findings support previous functional models based on dual-stream motor processing.

Conclusion: We constructed a preliminary model for the underlying structural interconnectedness of anatomic substrates involved in higher-order motor functioning which is seen impaired in IMA. Our model provides support for previous dual-stream processing frameworks discussed in the literature, but further clarification is necessary with voxel-based lesion studies of IMA to further refine these findings.

Keywords: dual stream; parcellation; tractography; ideomotor apraxia; tractography

1.0 INTRODUCTION

Apraxia refers to a broad dysfunction of skilled or learned movements, which is independent of damage to any motor or sensory networks [1]. One specific type of apraxia which was described in the early 1900s is ideomotor apraxia (IMA) and commonly occurs following stroke in the dominant (left) parietal lobe [1]. While numerous definitions have been proposed in the characterization of IMA, the general literature agrees that patients with IMA can display deficits in voluntary tool-related cognition, gesture imitation, and even fine motor control [2, 3]. Unfortunately, most reports of IMA are single case reports that implicate a variety of cortical regions which are often studied in isolation with highly specific tests, and therefore have subsequently precluded our effective study of the various anatomic substrates and functional roles in this praxis system [4].

Despite the variety of deficits implicated in IMA, some have proposed selective performance differences in skills of imitation versus pantomiming to verbal commands [5, 6]. Deficits may be more pronounced in pantomiming tool-use [7], but there are also deficits in the motor execution of tool-use as well [8]. Furthermore, others have suggested that these deficits can even be further divided based on if the action utilizes a familiar tool or a novel or abstract tool [9]. While some have contested such dissociations in ideomotor functions and the specific anatomic substrates involved [2], it is likely that the heterogeneity in IMA deficits can be best explained based on the selective differences in the particular cortices insulted in conjunction with the specific cortico-cortico connections that are disconnected between those cortices [10]. Anatomically, despite some mechanistic differences, both motor and cognitive theories implicate similar, yet large and non-specific regions in praxis functions and IMA deficits. They suggest a fronto-temporo-parietal network which is also thought to contain a dual-stream architecture of ventral and dorsal streams separated by their unique white matter connections [2, 11-13]. Recent improvements in neuroimaging data and computational algorithms

have provided unique opportunities to further refine an anatomic model supporting discussions on the structural interconnectedness of cortical regions involved in functions which are seen impaired in IMA patients [14].

Here, we construct create a highly detailed anatomic model of ROIs likely involved in an 'IMA network'. We utilized open-access meta-analytic software to generate activation likelihood estimations (ALEs) based on healthy fMRI studies reported in the literature in order to identify cortical regions which are seen functionally impaired in IMA. We then performed deterministic tractography on these relevant parcellations in 25 healthy individuals in order to understand how the parcellations may be structurally connected throughout the IMA network and support their functional relevance. We describe this model based on the cortical parcellation scheme published under the Human Connectome Project (HCP) with the goal of providing a detailed anatomic model of complex action cognition and execution related to IMA for future studies [14].

2.0 METHODS

2.1 Literature Search

A thorough literature search strategy was devised to screen through and selectively retrieve ROIs specific to ideomotor apraxia. The search was completed in the electronic databases PubMed and the BrainMap Sleuth 2.4.9-11 (functional database) from periods between 2017-2018. Searches focused on studies utilizing functional neuroimaging in healthy individuals. Given the heterogeneity of nomenclature surrounding ideomotor and ideational apraxia ('difficulty with sequential actions'), key-terms for both were incorporated into our search and then were independently reviewed and filtered to meet our inclusion criteria for ideomotor apraxia as stated above. Examples of some key words utilized in our many search

strings includes: “ideomotor apraxia, “pantomime,” “imitation,” “object manipulation,” “imagined movement.” References were also screened in favorable studies. Ultimately, PubMed yielded a total of 44 papers and Sleuth a total of 22 papers.

Functional MRI studies were included in our analysis if they fulfilled the following search criteria: (1) peer-reviewed publication, (2) task-based fMRI study related to object-related imagined movement, object manipulation, or pantomiming, (3) included standardized coordinate-based results in the Talairach or Montreal Neuroimaging Institute (MNI) coordinate space, and (4) included at least one healthy human control cohort. Of the 66 papers retrieved from our initial search, a total of 10 papers ultimately met our inclusion criteria following full-text reviews and were included in the activation likelihood estimation (ALE) [15-24]. These studies are represented in Table 1.

2.2 ALE Generation and Identification of Relevant Cortical Regions

BrainMap Ginger ALE 2.3.6 was used to extract the relevant fMRI data from the 10 included studies to create an activation likelihood estimation (ALE) [25]. All Talairach coordinates were converted to the MNI coordinate space using Ginger ALE. An ALE models the likely convergence of foci based on MNI coordinates and is commonly used in meta-analyses of neuroimaging data to demonstrate areas of activity that are associated with the task or brain network [25]. We subsequently performed a single study analysis using cluster-level interference in the MNI coordinate space (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. Such methodology has been

reiteratively applied and demonstrated by our team on other cortical areas with great reproducibility [26, 27].

2.3 Network Tractography

Cortices which are functionally co-activated and connected within a network tend to be structurally connected [28]. Thus, we proceeded to determine the backbone of the network using diffusion spectrum imaging (DSI)-based tractography. Publicly available imaging data from the Human Connectome Project were used for this study from the HCP database (http://humanconnectome.org, release Q3). Diffusion imaging with corresponding T1-weighted images from 25 healthy, unrelated subjects were analysed during fiber tracking analysis. A multi-shell diffusion scheme was used, and the b-values were 1000, 2000, and 3000 which were sampled in 90 directions. The in-plane resolution was 1.25 mm. The diffusion data was reconstructed using generalized q-sampling imaging with a diffusion sampling length ratio of 1.25 [29].

All brains were registered to the MNI coordinate space to standardize comparison between subjects. Tractography was performed in DSI Studio (Carnegie Mellon, http://dsi-studio.labsolver.org) using a two-ROI approach to initiate fiber tracking from a user-defined seed region, which consisted of our ALE-identified ROIs from healthy fMRI samples [30]. The angular threshold and maximum tract length for the tracts were 45 degrees and 800 mm, respectively.

2.4 Measuring Connection Strength

DSI studio was used to generate an adjacency matrix of connections between different ROIs and quantify strength between different of regions involved in transitive ideomotor

apraxia based on a random seed count of 2.5 million. The number of tracts between ROIs was recorded for each subject after fiber tractography was terminated. The strengths of the connections within the network were calculated by averaging the number of tracts between each ROI pair of the network across all subjects.

3.0 RESULTS

3.1 ALE Regions and Their Corresponding Parcellations

Figure 1a-d demonstrates the ALE of the 19 ideomotor apraxia-related, task-based fMRI experiments included in our meta-analysis. Regions of interest include the medial frontal gyrus (MFG), precentral gyrus extending into inferior frontal gyrus (IFG), angular gyrus, supramarginal gyrus (SMG), and precuneus. Six regions of interest were found to overlap the fMRI data, including the supplementary and cingulate eye field (SCEF), frontal operculum 4 (FOP4), medial intraparietal sulcus (MIP), anterior intraparietal sulcus (AIP), area 7 anterior-lateral (7AL), and area 7 postcentral (7PC) (Table 2). Comparison overlays between these cortical regions and the ALE are shown in Figure 2.

3.2 Structural Connections within the Ideomotor Apraxia Network

Deterministic tractography was utilized to show the basic structural connectivity of the IMA regions. Figure 3 demonstrates the major long-range white matter tracts that connect the different network areas; these include the inferior fronto-occipital fascicle (IFOF) and the frontal aslant tract (FAT). Figure 4 highlights the parietal parcellations identified in our cortical model which contained a collection of short-range, association fibers demonstrating a unique U-shaped morphology (“U-Fibers”).

To summarize the volume of structural interconnectedness of parcellations contained in the ideomotor apraxia network, a cortical model is provided in Figure 5 and the strength of individual connections shown in Table 3.

3.3 Fronto-Parietal Cluster of ROIs in the Ideomotor Apraxia Network

The cortical areas included in the apraxia model can be grouped into two general clusters: a frontal cluster (SCEF, FOP4) and a parietal cluster (7AL, 7PC, AIP, MIP). These ROIs were split amongst many short-range association fibers as well as long-rang connections as described below. Functional relevance is elucidated in detail in the *Discussion* section.

3.3.1 Short-Range Connections

U-shaped fibers form many of the connections between ROI pairs of the network (4/10 connections, 40%). These fibers generally have the same morphology, arising within one part of the cortex before curving 180 degrees to terminate in a part of the brain immediately adjacent to its origin. These U-shaped fibers represent the local intra-parietal connections between the superior parietal lobule and regions around the intraparietal sulcus.

3.3.2 Long-Range Connections

The predominant long-range fibers identified within our model are described below. They consisted almost entirely of IFOF connections (5/10 connections, 50%). Dense FAT connections were also strongly present in 5 of the 25 brains (1/10 connections, 10%).

4.0 DISCUSSION

We identified a fronto-parietal network connecting numerous ROIs described above in a probable apraxic-related motor cognition and action network which we deemed the "IMA network." Based on meta-analytic processing and deterministic tractography related to healthy functional neuroimaging data, we provide a comprehensive connectivity model of the anatomic substrates likely underlying the complex functions which are seen impaired in IMA. Further insight into the structural interconnectedness of anatomic substrates underlying IMA may provide further information lacking in models which focus on localized brain regions.

Previous models have differed in their selective characterizations of IMA and related functions due to heterogeneity in the literature concerning the characterization of specific cortices which may lead to such unique cognitive and visuomotor impairments. Furthermore, many have contextualized their findings in the setting of dual streams for higher motor processing, yet the underlying structural connectivity between specific cortices responsible for such functions remains incomplete and without adequate replication [12, 31, 32]. Therefore, we discuss the specifics of our proposed anatomic model in light of the functional relevance of possible dorso-dorsal and vento-dorsal streams explained in the literature [13], which may connect a variety of fronto-temporo-parietal brain networks to mediate selective higher-order motor functioning [13, 33]. Our model demonstrates strong concordance with previous models provided, but with further anatomic specificity of frontal and parietal regions not previously discussed, such as the structural connectedness of the superior parietal lobule [12, 32, 34]. We discuss the interconnectedness of identified ROIs in the IMA network in HCP nomenclature and how their structural connections may clarify functional IMA models previously proposed.

4.1 Frontal and Anterior Superior Parietal Cluster: SCEF and FOP4

4.1.1 Supplementary and cingulate eye fields (SCEF)

Area SCEF is a higher order oculomotor center located in the medial frontal cortex that regulates eye movements for goal-directed behavior [35]. We found that Area SCEF demonstrated structural connections to both frontal and parietal cortical regions. Short-range FAT fibers connected SCEF to a frontal opercular area FOP4 and long-range IFOF fibers connected SCEF to a parietal area known as MIP. SCEF was associated with the middle frontal gyrus ALE from the fMRI studies. According to the HCP parcellation scheme, SCEF is a new parcellation, but has been previously described to overlap with areas in the rostral portion of the supplementary motor area, the cingulate eye fields, and the supplementary eye fields. SCEF was one of four HCP parcellations defined as a supplementary motor area (SMA) and was notably the most significantly activated region in motor tasks. SCEF has also been more broadly referred to as a region within the premotor cortex (PMC), or area 6 [36].

Current literature regarding the precise function of SCEF is not clear, but demonstrates that it is activated during observation of others' movements and imagining ones' own self performing a movement and it also participates in a wide range of different oculomotor functions related to the selection, monitoring and control of visual behavior [37]. SCEF may be a critical frontal area involved in the dorso-dorsal pathway, which plays a role in online visuospatial processing of variable affordances [11, 38]. The dorso-dorsal pathway connects higher visual association and parietal visual areas, including MIP, to the dorsal PMC in order to provide automatically processed visuospatial information for quick sensorimotor control during actions involving objects [33, 38]. Indeed, the connections we found between SCEF and MIP appear to support this pathway as a key mediator in processing

variable affordances. Specifically, IFOF (IV) is thought to originate around the SCEF and middle frontal gyrus via the external/extreme capsules and our findings converge with previous studies illustrating the highly interconnectedness of this long-range fiber with fronto-parietal and occipital regions [32, 39]. While the dorsal visual processing stream remains separated from the ventral stream all the way up to frontal cortical areas such as the frontal eye field (FEF), these regions do not control gaze and instead the SCEF may influence neuronal activity in these areas to facilitate goal-directed visuospatial and visuomotor behavior, such as in following verbal commands [13, 37].

4.1.2 Frontal operculum 4 (FOP4)

Area FOP4 also demonstrated structural connections via IFOF to superior parietal areas known as MIP, 7AL, and 7PC. FOP4 is also a new parcellation, found superior and anterior to the insula [40]. FOP4 may represent a subdivision of the opercular part of IFG, classically known as Brodmann Area (BA) 44, as it is located just inferior to the area 44 parcellation in the HCP classification [14]. FOP4 was associated with the BA 44 or precentral gyrus ALE from the fMRI studies, although it seems to specifically correlate with the IFG, especially the pars opercularis, which was discussed in nearly all of the fMRI studies included in the current study as an area of debated necessity to transitive praxis actions. This region is activated in response to goal-oriented actions but has been implicated in planning gestures, planning pantomimes, manipulation of objects, imitation, and storing semantic knowledge necessary for tool use [41, 42].

Our results suggest that FOP4 may be an important frontal area for the dorsal pathway, but also strongly lends support for recent models discussing the importance of a ventro-dorsal stream possibly underlying a pantomime-specific pathway [32, 33, 38]. Compared

with the dorso-dorsal pathway, the ventro-dorsal pathway processes visuospatial input more slowly, integrates this information with semantic knowledge regarding the appropriate stable affordances (i.e., constant properties of tools), and projects to more ventral premotor areas, namely the pars opercularis of the IFG [33, 38]. Additionally, the ventro-dorsal pathway receives input from more inferior regions of the parietal cortex, including the anterior intraparietal sulcus which corresponds with the parcellation AIP [14, 33, 38]. However, we only found connections between FOP4 and AIP via IFOF in two of the 25 brains. Interestingly, both healthy and lesion studies suggest that selective tasks for pantomime actions alone may preferentially activate regions in the left (inferior) premotor and prefrontal areas, which includes FOP4 [32, 43]. Compared to the SCEF connections described above for visuomotor actions in imitation (IFOF-IV), a different division of the IFOF (IFOF-III) may mediate connections from frontal areas such as FOP4 and the IFG to parietal areas as shown in our cortical model to facilitate the additional cognitive processes required for guiding movement planning and pantomime.

1.2 Superior Parietal and Intraparietal Sulcus Cluster: 7PC, 7AL, MIP, AIP

4.2.1 Superior Parietal Areas 7PC and 7AL

Area 7PC demonstrated fairly consistent connections via intra-parietal U-shaped fibers with area MIP as well as participated in dense long-range IFOF fibers to FOP4. This parcellation has been classically described as a part of BA 7 within the superior parietal lobule (SPL) [14]. This region was more recently named 7PC according to cytoarchitectural studies, which described it as being the lateral portion of the anterior SPL, extending into the intraparietal sulcus anteromedially and the postcentral sulcus posteriorly [44]. 7PC and 7AL were associated with the SPL ALE from the fMRI studies. While inferior to area 7PC, area

7AL demonstrated similar connections to frontal and intra-parietal cortices, with the addition of area AIP. Area 7AL was considered a new parcellation by the HCP classification, although it was derived as the lateral area within 7A by the same cytoarchitectural studies which defined area 7PC [44]. Both areas 7AL and 7PC were associated with the SPL ALE from the fMRI studies.

Previous structural studies have been limited to analyzing the inferior parietal lobule [12]. Differently, the SPL can be organized into unique subregions allowing a diversity of function roles including somatosensory and visuospatial integration as well as attention, language, and working memory [27]. For instance, 7PC represents an anterior cluster that primarily guides visuomotor and observational processes while other adjacent superior parietal cortices may be more responsible for the actual motor output [45]. Previously, we have provided a cortical model of the dorsal attention network (DAN), which included areas outlined in the current cortical model, namely areas 7PC and AIP [27]. The DAN is responsible for voluntarily orienting attention which may support area 7PCs function in guiding visuomotor behavior following a verbal command in many IMA studies.

4.2.2 Intraparietal Sulcus Areas MIP and AIP

MIP demonstrated connections via all the major white matter tracts we documented. MIP showed short range connections via U-shaped fibers with AIP, 7AL, and 7PC and also demonstrated long-range connections with FOP4 via IFOF. As discussed in greater detail above, MIP had connections to SCEF, which may act as a part of the dorso-dorsal pathway. Although MIP is considered a new human cortical parcellation, it has been described in animal studies and is anatomically similar to its human analogue [14, 46]. MIP is found within the medial intraparietal sulcus (IPS), along with AIP, just posterior to other parietal ROIs

such as AIP, 7AL, and 7PC [14]. MIP was associated with the angular gyrus ALE from the fMRI studies.

AIP demonstrated connections via U-shaped fibers to areas MIP and 7AL and connections via the IFOF to area FOP4. Like MIP, AIP is also considered a new human cortical parcellation within the medial IPS, but has been previously described in animal studies which demonstrate its similarity to the human analogue of AIP [14, 46]. AIP was associated with the SMG ALE from the fMRI studies, though this is likely due to the close proximity of the IPS with the SMG. Importantly, AIP correlates with the anterior IPS, a region that plays a key role in the ventro-dorsal pathway, which is responsible for processing stable affordances [38]. As stated above, only two brains demonstrated connections that correlated with this pathway. AIP has also been suggested as the region connecting the dorso-dorsal and ventro-dorsal streams [38], which seems to correlate better with our findings, namely that AIP demonstrated much stronger connections to MIP.

4.5 Future Directions and Limitations

Coordinate-based meta-analyses allow the procuring of large amounts data reported in the literature regardless of heterogenous nomenclature utilized for homologous brain regions across different atlases. While other brain atlases exist, the HCP parcellation scheme is an established framework that can allow us to interpret and systematically study scientific findings in a common vernacular. However, it is important to consider that like all meta-analyses, the current study is inherently limited by the quality of the reported literature. Nonetheless, the use of rigorous statistical modelling as employed in the current study can allow others to also study previously isolated reports of disconnection syndromes like IMA together with high precision and in greater detail [25].

By performing DSI-based deterministic tractography on identified regions, we were also able to provide more accurate structural results compared to DTI-based studies that can be subsequently used to refine or analyze previous dual-stream frameworks proposed[47]. Such studies have not previously existed in the context of the superior parietal lobe especially, which is implicated in IMA related processes of dorsal-stream object localization and visuospatial processing [12]. However, a limitation of this method is that pathoanatomic differences exist between healthy and IMA impaired individuals. Such differences must be considered when interpreting the functional-structural inferences drawn from the current findings. A possible solution not utilized in the current study is to perform combined healthy fMRI-lesion analyses. Others should look to further refine our neuroanatomic connectivity model with similar combined structural-functional methodology but in reference to individual actions in order to provide further granularity of this praxis system for improved clinical understanding and subsequent treatments.

5.0 CONCLUSIONS

We constructed a detailed model of the anatomical substrates underlying the higher-order motor functioning seen impaired in ideomotor apraxia, which showed great concordance with previous models in the literature. Our 'IMA network' suggests a fronto-parietal network of ROIs which is predominantly a left IFOF system with numerous intra-parietal connections. A more accurate anatomical model has the potential to improve our neurological management of IMA and may provide further clarity on the distinct structural interconnectedness of cortical regions involved in high-order motor processing.

6.0 DISCLOSURES

Dr. Sughrue and Dr. Teo are co-founders of Omniscient Neurotechnology, however this does not pose a conflict of interest in this study. The other authors report no conflicts of interest.

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8.0 DATA AVAILABILITY

All data utilized in the current study have been provided in the current manuscript.

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FIGURE LEGENDS

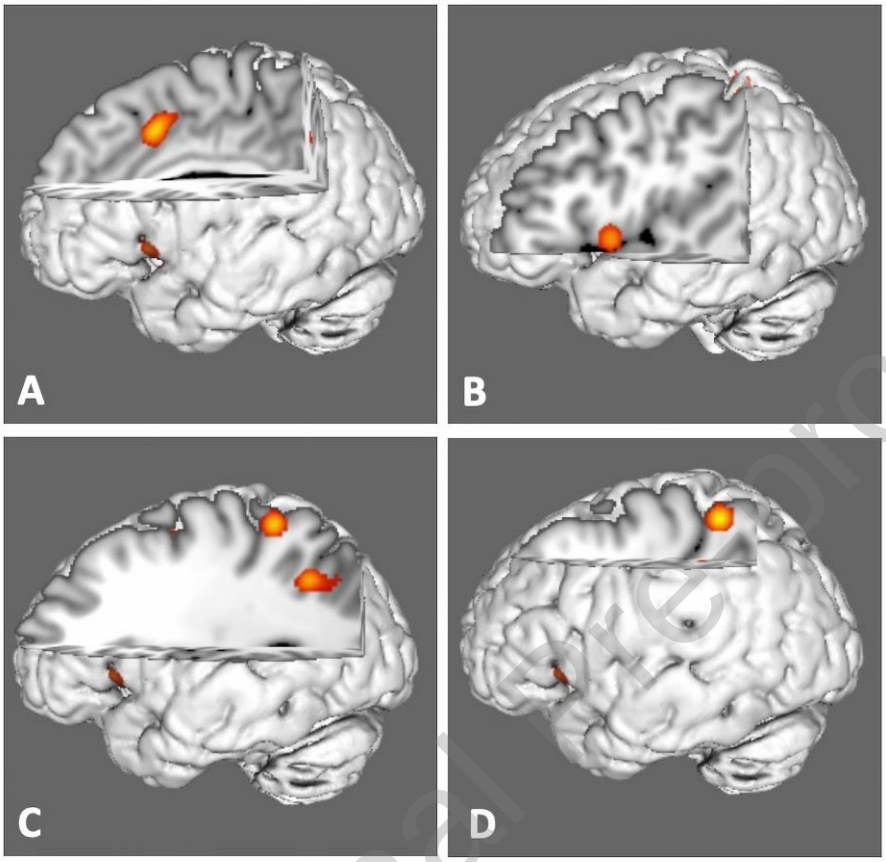

Figure 1. Activation likelihood estimation (ALE) of included studies utilizing task-based fMRI data (a-d). The three-dimensional ALE data are displayed in Mango on a brain normalized to the MNI coordinate space. (a) ALE data highlighting the medial frontal gyrus, (b) precentral gyrus, (c) precuneus, inferior parietal lobule, and (d) superior parietal lobule.

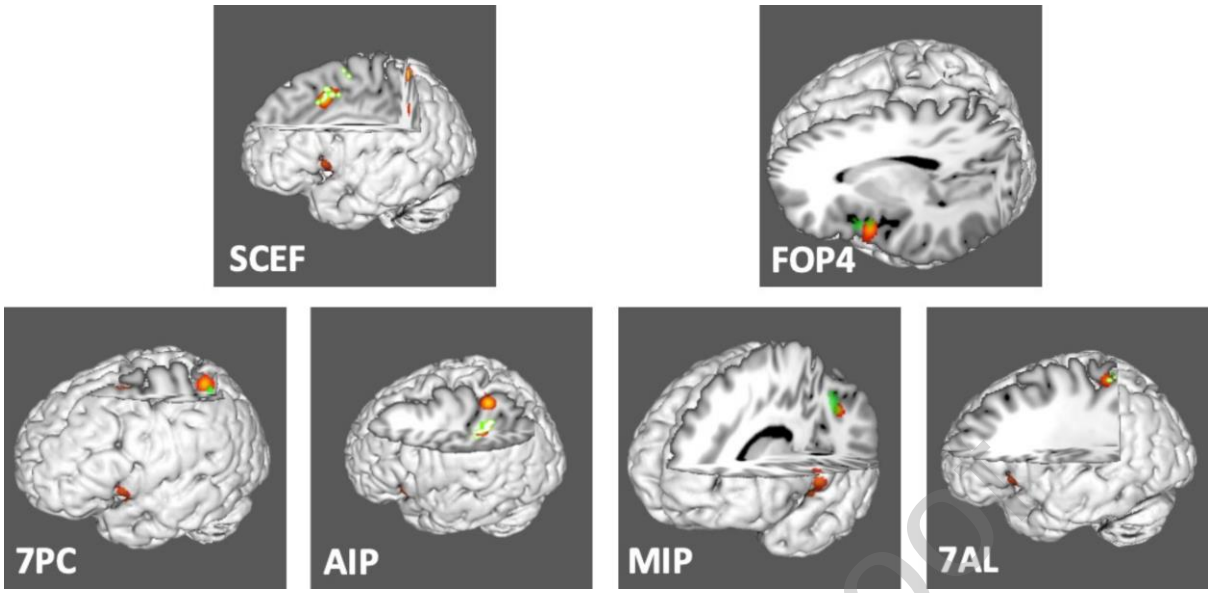

Figure 2. Comparison overlays between the cortical parcellation data (green) and activation likelihood estimation (ALE) data (red) from Figure 1 in the left cerebral hemisphere. Regions were visually assessed for inclusion in the network if they overlapped with the ALE data. Parcellations included in the model of the ideomotor apraxia network were identified in the frontal lobe including SCEF and FOP4 and 6a (top row) and the superior parietal lobule and intraparietal sulcus including 7PC, AIP, MIP and 7AL (bottom row). The labels indicate the parcellation shown in each panel.

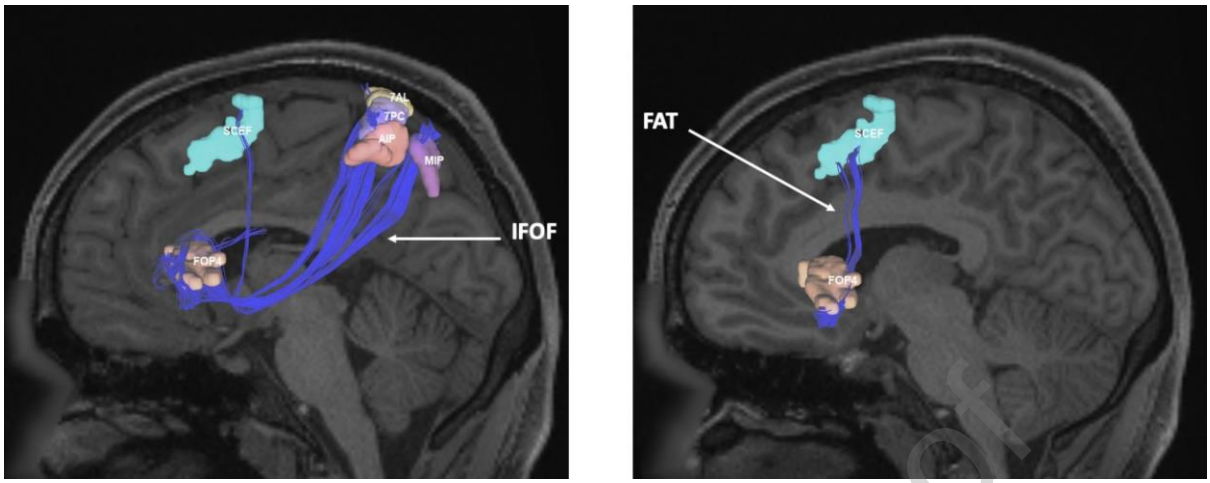

Figure 3. The major long-range white matter tracts associated with areas involved in the ideomotor apraxia network. Figure 3a shows the inferior fronto-occipital fascicle (IFOF). Figure 3b shows frontal aslant tract (FAT). Both tracts are shown in blue connecting unique parcellations shown in different colors.

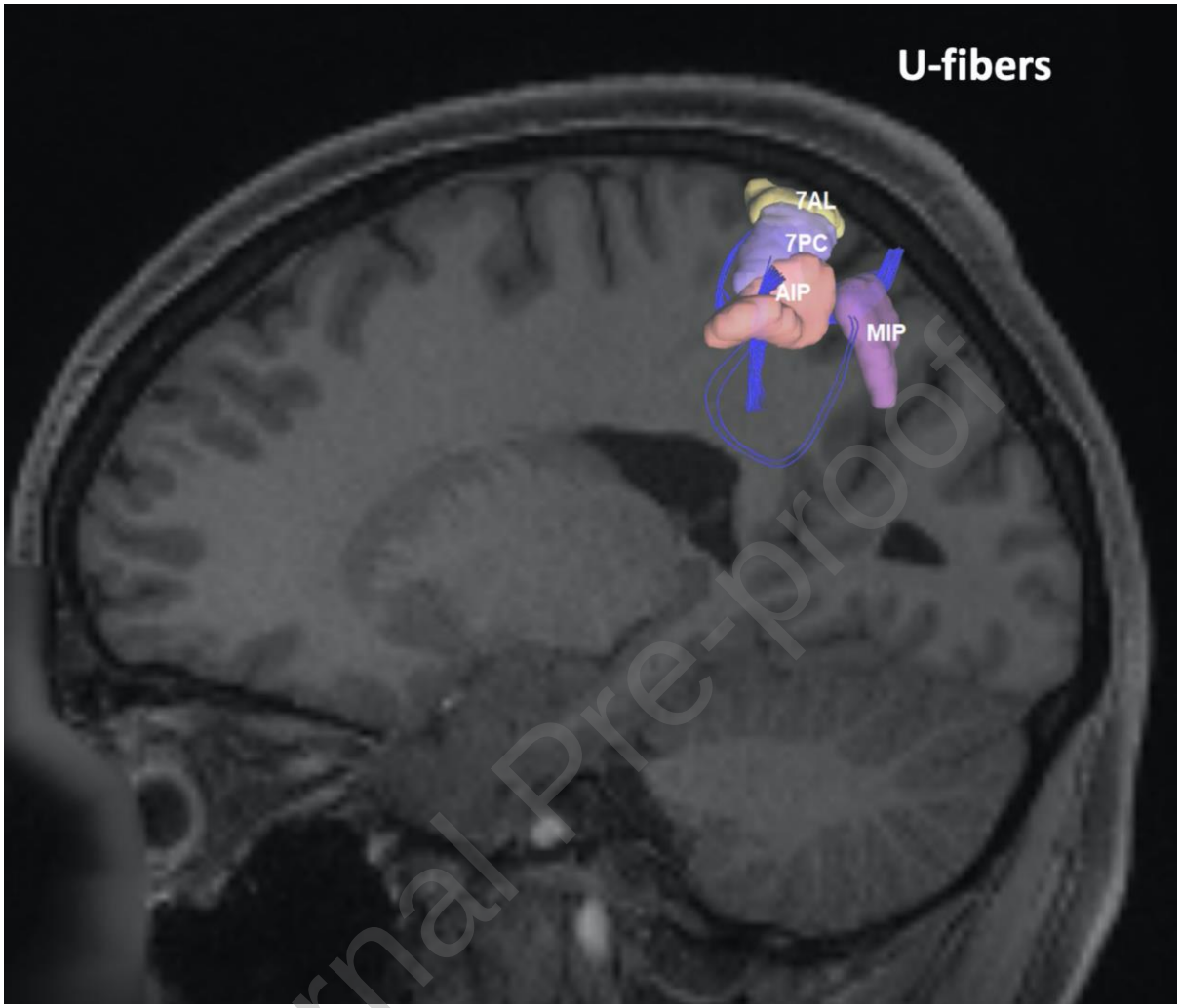

Figure 4. The major short range, intra-parietal association fibers involved in the ideomotor apraxia network. These fibers demonstrate a unique U-shaped morphology and are referred to as "U-fibers."

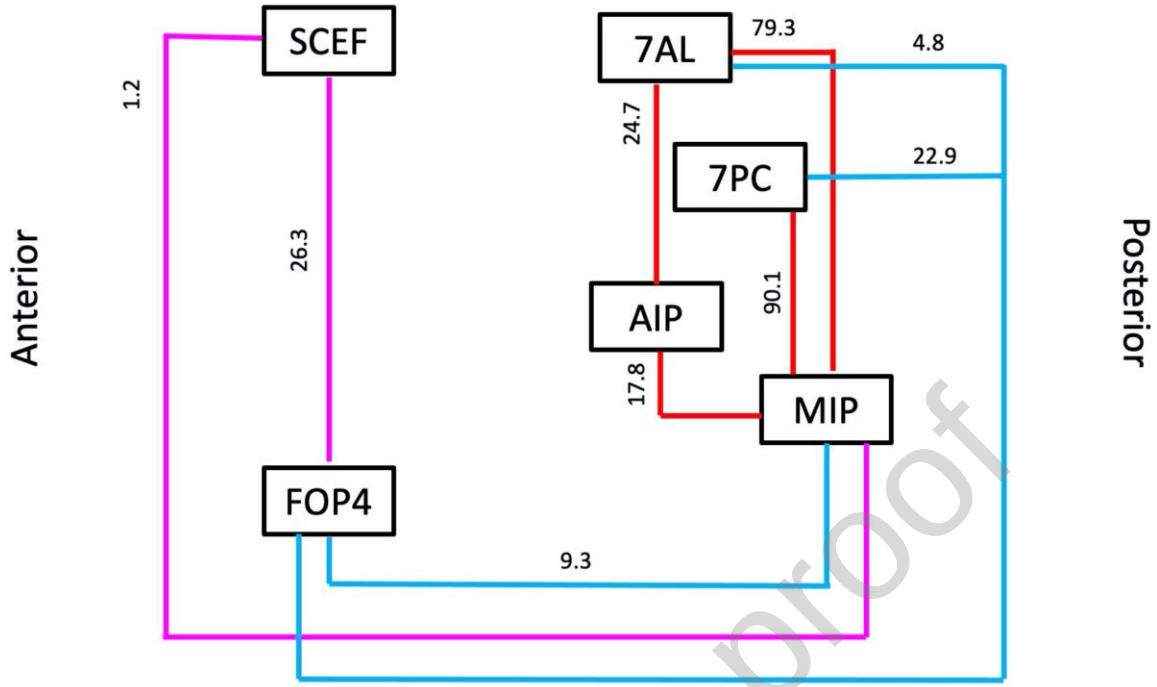

Figure 5. A cortical model of structural connectivity between identified regions of interest within the transitive ideomotor apraxia network. Different color tracts represent unique cortical connections. Tracts are labelled with the average number of fibers connecting two cortical regions.

Study	Task	Number of Participants	MNI/ Talairach	Coordinates		
Bohlhalter et al. 2009	Planning--preparation of right-hand transitive gestures	15/15 (100%)	MNI	34 -38 4 -36 32 -32 60 -56 40 -48	24 26 12 -8 -78 -70 -50 -54 -52 -52	-2 6 44 -54 36 38 -10 -22 -36 -28
Bohlhalter et al. 2009	Planning--preparation of left-hand transitive gestures	15/15 (100%)	MNI	46 -48 10 -6 -12 -30 32 -38 -56 40 -56	0 2 24 12 -4 -74 -68 -52 -68 -46 -60	36 32 24 32 72 44 40 36 -12 32 2
Bohlhalter et al. 2009	Execution of right-hand transitive gestures	15/15 (100%)	MNI	-42 -8 68 -32 54	-16 -12 -36 -50 -38	58 52 18 64 34
Bohlhalter et al. 2009	Execution of left-hand transitive gestures	15/15 (100%)	MNI	56 48 10 52 -64 -60	-20 -20 -2 14 -42 -28	46 60 62 -6 24 26
Creem-Regehr S H, 2005	Viewing Tools v. Shapes	12/12 (100%)	MNI	-36	-48	-22
Creem-Regehr S H, 2005	Imagined Grasping Tools v. Shapes	12/12 (100%)	MNI	-54 20 -60 -42 -38	-66 -52 -44 -68 -46	20 28 4 26 -20
Kubiak and Kroliczak 2016	Plan pantomime of object use when presented with gerundive verb for action	12/12 (100%)	MNI	-38 -4 -2 -46 -32 -14 -24 -32 58 4 2 12 24 30	-32 -10 6 4 -46 -18 -2 -56 8 -8 10 -4 0 -46	60 60 40 4 62 10 4 -26 12 58 36 12 6 -28
Lausberg et al. 2015	Pantomime tool use when presented with tool	15/15 (100%)	MNI	-61	-60	8
Maki-Marttunen et al. 2014	Transitive proximal gesture planning related	20/20 (100%)	MNI	-56 -42	6 10	8 30

	activity—right hand			-48	34	22
				-52	-10	46
				-20	-4	70
				-26	-60	42
				-38	-44	42
				52	6	34
				44	20	26
				34	20	6
				0	0	56
				10	10	44
				28	-60	40
				32	-76	24
				50	-38	6
Maki-Marttunen et al. 2014	Transitive distal gesture planning related activity—right hand	20/20 (100%)	MNI	-54	6	10
				-50	6	18
				-54	-6	46
				-48	36	14
				-46	42	26
				-6	8	50
				-26	-64	42
				-36	-46	40
				56	30	28
				30	-62	50
				22	-72	28
Maki-Marttunen et al. 2014	Transitive proximal gesture planning related activity—left hand	20/20 (100%)	MNI	-42	4	28
				-4	6	52
				-20	-4	74
				-32	24	4
				-28	-62	44
				-42	-44	46
				44	14	26
				34	24	0
				30	-72	48
				30	-70	36
Maki-Marttunen et al. 2014	Transitive distal gesture planning related activity—left hand	20/20 (100%)	MNI	-42	0	24
				-26	-78	32
				-28	-59	40
				46	14	30
				30	-70	34
				48	-72	-2
				23	-64	62
Ogawa and Imai 2016	Pantomime object use with RH when presented with picture of object	11/11 (100%)	MNI	-21	-94	2
				-39	-76	-16
				36	-55	-25
				27	-91	-11
				8	-7	-4
				24	-4	11
				-24	-13	-4
				-21	-1	8
				0	-1	65
				30	-55	-46
				-33	-52	-49
				-18	-16	59
				-39	-4	56
				45	2	50
				-30	-22	59
				45	-1	5
				-48	-34	32
				-36	5	5
				-36	-40	47

Passingham et al. 2014	Pantomime object use when presented with video of object pantomime and picture of object	8/8 (100%)	MNI	-49	-66	14
				-51	-49	18
				-24	-60	22
				-56	-22	36
				-48	-26	29
				-50	15	6
				-41	26	5
				-41	26	5
				-43	42	5
				-43	19	32
				-28	52	18
				49	-66	-4
				53	-48	11
				7	-57	44
				63	-27	25
				53	15	6
				54	23	3
				43	48	6
				34	28	26
Szameitat A J, 2007	Upper Extremity Transitive Movements vs. Baseline Resting Condition	15/15 (100%)	MNI	-4	10	47
				12	3	66
				32	-7	50
				-26	-7	63
				-42	-45	61
				-32	-47	67
				-63	-43	39
				59	-36	50
				63	-29	46
				51	-23	40
				20	-5	19
				20	-2	4
				-36	23	-6
Szameitat A J, 2007	Upper Extremity Transitive Movements vs. Whole Body Movements (Mixed Transitive and Intransitive Actions)	15/15 (100%)	MNI	65	-14	30
				53	-18	36
				51	-25	53
				-61	-14	34
				-67	-14	27
				40	-38	63
				32	-40	50
Vingerhoets et al. 2015	Pantomime hand shape associated with holding tool when presented with picture of tool	14/14 (100%)	Talarach	39.74	-7.07	62.67
				-2.44	5.55	62.14
				-48.4	-0.04	16.41
				4.04	5.57	62.03
				-48.37	27.49	23.77
				-51.28	-25.83	39.18
				-57.73	-23.42	42.42
				-47.97	-31.89	43.09
				61.94	-13.92	22.63
				-45.43	38.39	2.47
				-2.54	-1.77	52.78
				-58.26	13.13	8.55
				-64.25	-12.8	41.48
				-31.46	-45.92	64.37
				-41.29	-17.24	61.7
				36.46	-30.35	54.95
				-41.12	8.75	-4.75
				-64.31	-19.81	35.45
				-54.69	5.75	32.76
				-2.67	13.66	45.65
				-38.1	-37.3	53.54

				62.66 -54.59 -45.33	12.93 -24.13 45.71	-.21 34.59 11.83
Villiger et al. 2013	Observe and Imagine pantomime	14/14 (100%)	MNI	-6 -52 -58 12 -48 62 -54 44 -34 -22 -8 38	14 6 8 -62 -36 -32 -68 -76 10 0 -70 -60	44 2 4 56 34 22 2 0 8 12 -10 -28
Villiger et al. 2013	Observe and Imitate pantomime	14/14 (100%)	MNI	-2 -6 6 -50 60 -8 -60 58 -54 46 40 -20 -18 -38 40	-26 -12 4 6 8 -60 -24 -32 -72 -76 -12 -24 -74 -54 -58	66 6 46 2 2 64 12 30 0 2 -6 10 -22 -34 -30

Table. fMRI studies constituting the ideomotor apraxia network

Brain Parcellation	Coordinates in MNI Space			Cluster Size	Speculative Function
	x	***y***	***z***		
Supplementary Cingulate Eye Field (SCEF)	-4	7	50	$3mm^3$	Oculomotor control of goal directed visuospatial and visuomotor behavior
Frontal Operculum 4 (FOP4)	-54	9	6	$5mm^3$	Planning gestures and pantomime; semantic storage; processing and initiation of language
Area 7 Anterior Lateral (7AL)	-41	-43	53	$2mm^3$	Attentional and visual processing; self-centered mental imagery
Area 7 Postcentral (7PC)	-27	-62	43	$3mm^3$	Visual and somatosensory processing; guiding visuomotor behavior; language and working memory
Anterior Intraparietal (AIP)	-38	-44	43	$4mm^3$	Object recognition, processing, and grasping; visuospatial processing
Medial Intraparietal (MIP)	-27	-59	41	$2mm^3$	Manipulation of objects in space; transforms visual information for precise arm-movement and prehension

Table 2. Anatomical and functional descriptions of the regions of interest included in our ideomotor apraxia (IMA) network. Abbreviations: MNI, Montreal Neurological Institute; mm, millimeter

Connection	# of Brains (Total = 25 brains)	Tracts/All Brains	Avg. Tracts/ Brain	Connection Type
SCEF to FOP4	5	26.3	(658/5) 131.6	FAT
SCEF to MIP	5	1.2	(30/5) 6	IFOF (IV)
FOP4 to MIP	5	9.3	(233/5) 46.6	Likely IFOF (III)
FOP4 to AIP	2	12.5	(313/2) 156.5	IFOF (III)
FOP4 to 7AL	8	4.8	(120/8) 15	IFOF (III)
FOP4 to 7PC	5	22.9	(572/5) 114.4	IFOF (III)
MIP to AIP	9	17.8	(445/9) 49.4	U-Shaped Fiber
MIP to 7AL	13	79.8	(1995/13) 153.5	U-Shaped Fiber
MIP to 7PC	16	90.1	(2252/16) 140.8	U-Shaped Fiber
AIP to 7AL	7	24.7	(617/7) 88.1	U-Shaped Fiber

Table 3. Ideomotor apraxia network connections.

CRediT Statement

Christen M. O'Neal: Investigation, Writing – Original Draft. **Syed A. Ahsan**: Formal Analysis, Validation. **Nicholas B. Dadario**: Writing – Review & Editing, Validation. **R. Dineth Fonseka**: Data Curation, Investigation. **Isabella M. Young**: Writing – Review & Editing, Visualization. **Allan Parker**: Methodology. **B. David Maxwell**: Software. **Jacky T. Yeung**: Writing – Review & Editing. **Robert G. Briggs**: Methodology, Project Administration. **Charles Teo**: Supervision. **Michael E. Sughrue**: Conceptualization, Supervision.

Highlights

- We constructed a model of the structural connectivity involved in ideomotor apraxia.
- We used meta-analytic methods to determine regions of interest involved in this network.
- Deterministic tractography was used to determine the structural connectivity.
- A fronto-parietal network was found consisting mainly of intra-parietal U-shaped fibers.
- Our model provides support for previous dual-stream processing frameworks.