The Structural Connectivity of The Human Angular Gyrus as Revealed by Microdissection and Diffusion Tractography

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Abstract

The angular gyrus (AG) has been described in numerous studies to be consistently activated in various functional tasks. The angular gyrus is a critical connector epicenter linking multiple functional networks regarding its location in the posterior part of the inferior parietal cortex, namely at the junction between the parietal, temporal, and occipital lobes. It is thus crucial to identify the different pathways that anatomically connect this high-order association region to the rest of the brain. Our study revisits the three-dimensional architecture of the structural AG connectivity by combining state-of-the-art postmortem blunt microdissection with advanced in vivo diffusion tractography to propose a comprehensive description of the association, projection, and commissural fibers that connect the human angular gyrus. AG appears as a posterior "angular stone" of associative connections belonging to mid- and long-range dorsal and ventral fibers of the superior and inferior longitudinal systems, respectively, to short-range parietal, occipital and temporal fibers including U-shaped fibers the posterior transverse system. Thus, AG is at a pivotal dorso-ventral position reflecting its critical role in the different functional networks, particularly in language elaboration and spatial attention and awareness in left and right hemispheres, respectively. We also reveal striatal, thalamic, and brainstem connections and a typical inter-hemispheric homotopic callosal connectivity supporting the suggested AG role, in the integration of sensory input for modulating motor control and planning. The present description of AG's highly distributed wiring diagram may drastically improve intraoperative subcortical testing and post-operative neurologic outcomes related to surgery in and around the angular gyrus.

Introduction

With its location in the postero-dorsal portion of the inferior parietal cortex, namely at the junction between the parietal, temporal, and occipital lobes, the angular gyrus (AG) is a critical connector epicenter linking numerous functional networks involved in semantic processing, word reading, and comprehension, number processing, default mode network, memory retrieval, attention and spatial cognition, reasoning, and social cognition (Seghier 2013). It is thus crucial to identify the different tracts that anatomically connect this high-order association region to the rest of the brain.

From the most fundamental point of view, the white matter is organized in fiber tracts, aggregating axons running in close apposition to each other and sharing cortical and/or subcortical origins and destinations. The complex connections and pathways arising from the brain can be reduced to a series of organizational principles (Schmahmann and Pandya 2006; Nieuwenhuys et al. 2008). Every cortical area is linked with other cortical and subcortical regions by pathways grouped into three distinct categories initially defined by Meynert (Meynert 1885): association, commissural, and projection fibers. The complexity of connections and pathways arising from AG can thus be reduced to such a relatively simple schema. The angular gyrus would be therefore linked with other cortical and subcortical areas by pathways grouped into (1) association fibers traveling to other ipsilateral cortical areas from the shortest U-shaped fibers connecting the neighborhood cortical areas to the long-range pathways, (2) commissural fibers passing to the contralateral hemisphere, (3) projection fibers coursing to the basal ganglia, thalamus, and brainstem structures.

Our study describes the angular gyrus's comprehensive clinically actionable structural connectivity by utilizing diffusion magnetic resonance imaging (dMRI)-based tractography in a large cohort of 411 healthy participants and validation with modified Klingler-based anatomical microdissection as ground truth.

Materials And Methods

MRI acquisitions and whole-brain tractography

Diffusion-weighted (DWI) and T1-weighted images of 411 healthy participants from the BIL&GIN database were used (mean age of 29.9 ± 7.9 years; 53% women; 49% left-handers) (Mazoyer et al. 2016). All participants gave written consent before participation in the study, approved by the local ethics committee (CCPRB Basse-Normandie). High-resolution 3D T1 weighted images were obtained using a 3D-FFE-TFE sequence (TR, 20 ms; TE, 4.6 ms; flip angle, 10°; inversion time, 800 ms; turbo field echo factor, 65; Sense factor, 2; field of view, 256 × 256 × 180 mm; isotropic voxel, 1x1x1 mm^3). DWI data were acquired using a single-shot spin-echo echo-planar sequence composed of one b_0 map ($b = 0\ s/mm^2$) followed by 21 diffusion gradient maps ($b = 1000\ s/mm^2$) homogeneously spread over a half-sphere and the 21 opposite directions spread over the opposite half-sphere. A second series with the same features was acquired to increase the signal-to-noise ratio. Seventy axial slices parallel to the AC-PC plane were acquired from the bottom of the cerebellum to the vertex with the following imaging parameters: TR = 8500 ms; TE = 81 ms; angle = 90°; SENSE reduction factor = 2.5; a field of view 224 mm; acquisition matrix 112 × 112, 2 mm isotropic voxels.

A whole-brain tractogram was built for each participant by using the TractoFlow diffusion MRI processing pipeline (Theaud et al. 2020), based on Nextflow (Di Tommaso et al. 2017) and Singularity (Kurtzer et al. 2017) or Docker (link) containers. It consists of 15 tasks, from the basic preprocessing steps on diffusion-weighted and T1-weighted images to tract the WM pathways. We used the default parameters to compute a whole-brain tractogram using the probabilistic method of the anatomically-constrained particle filter tracking algorithm (Girard et al. 2014) with ten seeds per voxels and seeded from the whole WM mask.

Each T1-weighted image was normalized to the MNI space using ANTS (Avants et al. 2009). Therefore, the affine transformation and nonlinear deformation were applied to warp the whole-brain tractogram to the MNI space.

Automatic extraction of whole-brain anatomically-plausible streamlines

We split the WM fibers included in a whole-brain tractogram into anatomically plausible or implausible fibers using ExTractorflow (Petit et al. 2019). ExTractorflow is a rule-based automatic pipeline that filters out false-positive streamlines from tractograms by following brain neuroanatomy organizational principles (Meynert 1885; Dejerine and Dejerine-Klumpke 1895, 1901; Ludwig and Klingler 1956; Crosby et al. 1962; Schmahmann and Pandya 2006; Nieuwenhuys et al. 2008). First, every cortical area is linked with other cortical and subcortical regions by pathways grouped into three distinct categories, namely the association, commissural, and projection fibers. Second, the commissural, projection, and long-range association fibers travel within the central WM part of the core of a gyrus, namely the gyral stem, and therefore never from the side of a gyrus by crossing a sulcus. Third, the shorter U-shaped association fibers connect adjacent gyri by running in a thin band immediately beneath the GM, constituting the most external part of the gyral stem. Following these anatomical principles, regions of interest (ROIs) from the Johns Hopkins University (JHU) template (Oishi et al. 2009) are used to define ROI-based sequential filtering conditions. ExTractor starts, therefore, by considering a streamline as anatomically-implausible when shorter than 20 mm, or making a loop with an angle of more than 360° or was a broken streamline with at least one termination within the deep WM structures or terminating along the ventricles (Fig. 1A).

Interestingly, the JHU template includes both cortical gray matter and underlying superficial white matter parts for each gyrus. By manipulating these different ROIs, it is possible to create additional ROIs that optimize the filtering of anatomically plausible fibers while applying the principles of WM fiber organization emanating from a given gyrus. Two additional ROIs were thus used for each gyrus and each hemisphere. The first one corresponds to the outermost part of the gyrus, namely its GM shell (AG_{shell}, Fig. 1B). The second corresponds to the "entrance/exit door" of the gyrus, namely its WM stem (AG_{stem}), which was manually drawn between the shell boundaries corresponding to the fundus of the sulci delimiting the gyrus. An essential step in ExTractorflow is to consider as plausible fibers only those ending in a gyrus while having passed through the stem and not crossing the shell. A final series of filtering is applied on each type of stem/shell-based streamlines to remove spurious ones with ROI-based sequential filtering rules. The remaining commissural, projection, and association (including U-shaped) streamlines thus compose a final anatomically-plausible whole-brain tractogram (Fig. 1A).

Virtual dissection of WM connections of the angular gyrus

The virtual dissection of the structural AG connectivity was performed on the 411 anatomically-plausible whole-brain tractograms. We first considered only streamlines with one cortical termination in the left and right angular gyri, passing through the AG_{stem} and not crossing the AG_{shell} (Fig. 1B). Association angular fibers were composed of the streamlines with the other termination in any other ipsilateral gyrus, passing through its stem and not crossing its shell. Projection angular fibers were composed of the streamlines with the other termination either in the putamen, caudate nucleus, thalamus, or the brain stem. Homotopic commissural angular fibers were composed of the streamlines ending in left and right AG.

AG tractography data analysis

Averaged MNI coordinates of the center of gravity of the fibers termination of each AG pair were computed in each subject, therefore reported (mean ± standard deviation) over the total number of participants in Table 1. Similarly, averaged length, area, volume, and shape descriptors of each AG pair were also computed in each participant using the shape analysis method (Yeh 2020) and are reported in Supplementary Table 1. This describes the between-subject variations of macroscopic structural features of the multiple types of angular fiber pathways. Note that a given tract is considered present in a subject if at least 5 streamlines compose it. Thus, a tract present in a smaller number of participants can be regarded as "hard-to-tract" because of anatomical constraints that are pitfalls for the tractography algorithms, *e.g.*, high rate of fiber crossings and bottlenecks (Rheault et al. 2020; Schilling et al. 2021).

Table 1
Mean (± standard deviation) of MNI coordinates of the AG tracts

			Angular gyrus			Opposite termination		
			X	Y	Z	X	Y	Z
Long-range fronto-dorsal	**IFG**	**L**	-45.0 ± 3.2	-58.7 ± 3.0	+ 43.5 ± 3.4	-49.3 ± 1.7	+ 18.0 ± 3.4	+ 11.7 ± 3.0
		R	+ 47.4 ± 2.6	-56.7 ± 2.8	+ 40.3 ± 3.9	+ 50.5 ± 2.0	+ 23.5 ± 3.9	+ 9.5 ± 3.8
	MFG	**L**	-41.7 ± 2.8	-60.7 ± 2.9	+ 45.9 ± 2.5	-38.7 ± 2.0	+ 17.6 ± 6.8	+ 41.0 ± 7.5
		R	+ 44.7 ± 2.8	-59.4 ± 2.9	+ 41.7 ± 3.9	+ 40.1 ± 1.9	+ 25.5 ± 7.5	+ 33.3 ± 8.5
	PrCG	**L**	-42.5 ± 2.7	-59.9 ± 2.8	+ 45.3 ± 2.5	-47.8 ± 5.1	-6.1 ± 3.9	+ 40.1 ± 8.2
		R	+ 44.1 ± 2.5	-58.7 ± 2.8	+ 43.1 ± 3.2	+ 50.4 ± 3.3	-2.1 ± 2.7	+ 38.1 ± 5.7
Long-range fronto-ventral	**IFG**	**L**	-47.1 ± 3.4	-59.5 ± 3.2	+ 41.3 ± 4.5	-45.4 ± 1.6	+ 32.9 ± 2.0	-4.7 ± 2.6
		R	+ 46.3 ± 3.5	-61.4 ± 3.2	+ 38.1 ± 4.9	+ 45.6 ± 2.5	+ 32.9 ± 2.2	-5.7 ± 3.1
	MFG	**L**	-47.2 ± 3.2	-59.8 ± 2.3	+ 39.9 ± 4.2	-36.3 ± 2.0	+ 50.9 ± 2.9	+ 2.5 ± 7.1
		R	+ 47.4 ± 3.4	-60.2 ± 3.6	+ 37.6 ± 4.4	+ 38.0 ± 2.2	+ 52.3 ± 2.2	-3.4 ± 4.8
	SFG	**L**	-46.6 ± 2.9	-59.6 ± 2.7	+ 41.4 ± 3.8	-12.6 ± 2.2	+ 59.6 ± 4.0	+ 14.2 ± 8.9
		R	+ 47.0 ± 3.6	-60.8 ± 3.3	+ 37.4 ± 5.3	+ 13.9 ± 2.1	+ 62.3 ± 2.8	+ 9.4 ± 7.0
	FrOrb	**L**	-47.1 ± 3.3	-59.3 ± 2.6	+ 40.8 ± 4.2	-20.6 ± 2.0	+ 36.7 ± 6.1	-14.9 ± 1.5
		R	+ 46.8 ± 3.5	-60.7 ± 3.6	+ 38.0 ± 5.1	+ 22.6 ± 2.8	+ 37.3 ± 5.0	-14.4 ± 1.6
	Insula	**L**	-41.6 ± 3.3	-59.9 ± 8.8	+ 44.6 ± 7.1	-35.1 ± 1.7	-12.0 ± 7.6	+ 7.9 ± 7.0

Supplementary Table 1. Mean (± standard deviation) values of shape descriptors for each AG pathway

A. Long-range fronto-dorsal AG connectivity

			Angular gyrus			Opposite termination		
		R	+ 46.4 ± 3.8	-59.4 ± 4.7	+ 38.1 ± 5.9	+ 35.7 ± 1.2	-10.5 ± 3.9	+ 7.4 ± 3.3
Short-range Parietal	**PoCG**	**L**	-42.9 ± 3.3	-60.1 ± 4.0	+ 45.6 ± 3.5	-43.3 ± 6.2	-26.5 ± 4.2	+ 54.8 ± 6.2
		R	+ 43.9 ± 3.0	-58.9 ± 3.3	+ 44.5 ± 3.3	+ 45.8 ± 4.9	-22.5 ± 4.0	+ 51.6 ± 4.6
	PrCu	**L**	-38.7 ± 4.2	-66.4 ± 4.2	+ 46.7 ± 2.5	-9.9 ± 1.2	-67.6 ± 2.9	+ 52.4 ± 4.0
		R	+ 39.5 ± 4.5	-65.5 ± 5.0	+ 46.4 ± 2.8	+ 11.2 ± 0.9	-67.8 ± 3.6	+ 52.6 ± 4.7
	SMG	**L**	-45.8 ± 3.5	-57.1 ± 3.1	+ 43.5 ± 4.1	-53.6 ± 3.6	-38.1 ± 3.4	+ 41.4 ± 3.9
		R	+ 48.9 ± 3.5	-54.3 ± 3.3	+ 38.6 ± 6.1	+ 58.1 ± 2.2	-34.0 ± 3.4	+ 36.9 ± 5.4
	SPG	**L**	-39.6 ± 2.9	-62.1 ± 3.4	+ 46.9 ± 2.0	-25.3 ± 2.6	-60.1 ± 3.8	+ 56.3 ± 2.0
		R	+ 41.4 ± 3.4	-59.9 ± 4.5	+ 45.7 ± 2.3	+ 25.6 ± 2.3	-59.5 ± 3.9	+ 56.5 ± 2.1
Short-range Occipital	**SOG**	**L**	-35.4 ± 4.4	-70.0 ± 3.7	+ 44.1 ± 2.4	-18.6 ± 1.6	-82.9 ± 2.2	+ 35.4 ± 2.8
		R	+ 36.5 ± 4.9	-69.3 ± 3.5	+ 43.3 ± 4.3	+ 17.8 ± 1.5	-81.6 ± 2.2	+ 37.3 ± 2.6
	MOG	**L**	-38.9 ± 5.3	-65.8 ± 4.2	+ 42.7 ± 3.8	-39.8 ± 2.8	-75.8 ± 2.8	+ 27.4 ± 3.2
		R	+ 37.9 ± 4.9	-66.2 ± 3.7	+ 40.4 ± 5.6	+ 39.9 ± 2.6	-74.9 ± 2.5	+ 24.8 ± 4.3
	IOG	**L**	-43.3 ± 4.6	-65.6 ± 4.7	+ 40.1 ± 3.4	-49.7 ± 2.2	-68.1 ± 2.5	-1.1 ± 2.0
		R	+ 43.0 ± 3.8	-66.2 ± 3.2	+ 36.2 ± 5.0	+ 51.3 ± 2.2	-62.0 ± 1.8	0.0 ± 3.0
Short-range Temporal	**STG**	**L**	-50.1 ± 2.6	-57.6 ± 2.3	+ 36.7 ± 3.5	-56.7 ± 2.4	-36.7 ± 4.7	+ 10.4 ± 3.5
		R	+ 51.0 ± 2.8	-57.5 ± 3.6	+ 30.5 ± 4.8	+ 56.2 ± 3.7	-27.1 ± 4.6	+ 4.9 ± 2.6

Supplementary Table 1. Mean (± standard deviation) values of shape descriptors for each AG pathway

A. Long-range fronto-dorsal AG connectivity

			Angular gyrus			Opposite termination		
	MTG	L	-50.2 ± 2.2	-58.0 ± 1.8	+ 36.0 ± 3.3	-58.2 ± 1.1	-49.2 ± 4.0	+ 0.9 ± 3.5
		R	+ 50.5 ± 2.2	-58.4 ± 2.8	+ 33.3 ± 3.9	+ 58.6 ± 1.2	-47.2 ± 3.3	+ 0.2 ± 2.9
	ITG	L	-51.6 ± 2.3	-58.4 ± 2.3	+ 34.2 ± 3.6	-54.6 ± 2.0	-40.6 ± 6.6	-19.9 ± 2.9
		R	+ 50.0 ± 2.5	-62.0 ± 2.5	+ 30.9 ± 4.1	+ 53.2 ± 1.9	-39.1 ± 4.3	-20.6 ± 2.5
Projection fibers	Putamen	L	-45.7 ± 3.4	-59.0 ± 3.0	+ 44.1 ± 3.6	-29.2 ± 0.2	-19.3 ± 0.8	+ 0.7 ± 0.9
		R	+ 44.3 ± 3.9	-60.9 ± 3.9	+ 43.3 ± 4.5	+ 31.1 ± 0.4	-15.5 ± 0.8	-1.5 ± 1.3
	Thalamus	L	-46.5 ± 3.2	-58.3 ± 2.9	+ 43.8 ± 3.9	-18.1 ± 1.2	-28.6 ± 0.9	+ 5.7 ± 2.1
		R	+ 43.8 ± 4.6	-60.7 ± 4.2	+ 43.4 ± 4.3	+ 19.2 ± 1.2	-28.0 ± 0.6	+ 4.4 ± 1.8
	Pons	L	-38.4 ± 3.4	-65.8 ± 3.6	+ 45.3 ± 2.0	-6.1 ± 1.4	-30.7 ± 0.9	-39.1 ± 3.1
		R	+ 41.0 ± 3.6	-63.9 ± 3.3	+ 42.4 ± 3.4	+ 6.5 ± 1.3	-30.7 ± 0.8	-41.1 ± 2.6
	Midbrain	L	-38.3 ± 4.1	-65.5 ± 4	+ 44.7 ± 2.3	-10.1 ± 0.9	-27.1 ± 0.9	-9.3 ± 0.8
		R	+ 39.8 ± 4.2	-64.3 ± 4.4	+ 42.7 ± 4.1	+ 11.9 ± 1.9	-26.1 ± 2.3	-9.1 ± 2.3
Corpus Callosum			-41.8 ± 4.7	-63.4 ± 4.9	+ 44.1 ± 2.7	+ 42.9 ± 4.5	-61.6 ± 5.5	+ 42.7 ± 3.9

Supplementary Table 1. Mean (± standard deviation) values of shape descriptors for each AG pathway

A. Long-range fronto-dorsal AG connectivity

Postmortem dissection of AG

We included pictures of micro-dissections of 8 hemispheres (5 left and 3 right) included in the Brain Anatomy Data Bank (BADaBank) of the Structural and Functional Connectivity Lab Project, performed at the Department of Neurosurgery of the "S. Chiara" Hospital (Azienda Provinciale per i Servizi Sanitari, Trento, Italy). According to the protocols approved by the Ethical Committee of the APSS (N° 06/2018), after extraction of the brain hemispheres, the specimens were arranged with injection in carotids and vertebral arteries with and immersion in formalin 10% for 40 days. The formalin immersion was followed by gently removing vessels and arachnoids and a first freezing process at -80°C for at least 20 days (maximum 30 days). After a cautious decortication according to the cortex sparing technique (Martino et al. 2010), the specimens were submitted to re-immersions in formalin 10% and frost-defrost cycles following the different layer by layer dissection technique. This modified Klingler's preparation was developed to improve the penetration of the formalin in the deep layers and improve the visualization and separation even of the deeper fibers (Sarubbo et al. 2016; Maffei et al. 2019). Finally, the results of the micro-dissections were confirmed by the 3D exploration of photogrammetric step-by-step multilayer dissection in eleven 3D-hemispheres models (5 left and 6 right), according to the previous technique described by our group (De Benedictis et al. 2018; Mahdy Ali and Avesani 2021).

Results

The AG is structurally connected to distinct cortical and subcortical areas in the human brain. We have identified 22 different bilateral AG tracts to which we must add homotopic callosal fibers connecting both left and right angular gyri (Figs. 2). The AG is connected with the frontal lobe through both dorsal and ventral long-range association fibers, the parietal, occipital, and temporal lobes through an abundance of short-range (including U-shaped) association fibers, and with the thalamus, putamen, midbrain, and pons through projection fibers. Figure 3 highlights the connectivity pattern of the fibers association tracts terminating in AG. The shape of the colored lines represents the general path morphology of these long- and short-range association tracts. It corresponds to the centroid of the concatenated WM fibers extracted over the 411 participants for each AG tract. The thickness of the colored lines corresponds to the averaged diameter of each AG tract estimated with the shape analysis (Suppl. Table 1). Figures 4 to 10 (except Fig. 9) show both tractography- and dissection-based representation of the different AG tracts except for the homotopic callosal, midbrain, and pons fibers that require a particular dissection approach envisaged in further studies. Figure 9 highlights the tripartite organization of the termination of the short-range fibers in AG.

Long-range association angular fibers (Figs. 3, 4, and 5)

Regarding the long-range association pathways, the angular gyrus is predominantly connected to the frontal cortex via the dorsal pathway of the superior longitudinal system (SLS, (Mandonnet et al. 2018). Fronto-dorsal AG connections were identified with the inferior frontal (IFG), middle frontal (MFG), and precentral (PrCG) gyri in the 411 subjects for both hemispheres (Figs. 3 and 4). They correspond to the most extensive AG tracts in volume, whole areas, and diameter (Suppl. Table 1). The three fronto-dorsal AG tracts lie between the superior convexity of the frontal cortex, run above the superior limiting sulcus of the insula, and terminate in the superior part of AG (Fig. 3). They follow a medio-lateral distribution, from the most medial route for the AG-MFG tract to the most lateral one for the AG-IFG tract. AG-MFG corresponds to the SLF-II sub-component of SLS, while AG-PrCG and AG-IFG belong to the SLF-III sub-component, as previously described (Wang et al. 2016). We recently reviewed the hodology of the SLS of the human brain (Vavassori et al. 2021) and found the involvement of the angular gyrus as part of the definition of the SLS (*i.e.*, SLF/AF complex) since Dejerine (Dejerine and Dejerine-Klumpke 1895).

Whatever the nomenclature of SLF sub-components used for more than a century, the angular gyrus has been consistently described as connecting MFG, PrCG, and IFG via the dorsal pathway (Cf. Figures 5,7 and 8 in (Vavassori et al. 2021)).

The angular gyrus is also connected, but to a lesser extent, to the frontal cortex via the ventral pathway of the inferior longitudinal system (ILS, (Mandonnet et al. 2018). Fronto-ventral AG connections were identified with the anterior part of the superior frontal gyrus (SFG), and the ventral parts of MFG and IFG, up to the fronto-orbital gyri (FrOrbG) (Figs. 3 and 5). They run under the anterior limiting sulcus of the insula, in the external capsule, and continue under the inferior limiting sulcus of the insula before turning within the anterior part of the *stratum sagittale* (SS) and terminate in the inferior part of AG. It corresponds to the inferior fronto occipital fascicle (IFOF), namely the deepest layer of the ILS, as previously described in tractography and dissection (Wu et al. 2016a; Wang et al. 2013; Palejwala et al. 2020; Di Carlo et al. 2019) (see also a recent review (De Benedictis et al. 2021). Figure 3 also shows that the main route of the fronto-ventral AG tracts run deeper than the main route of the short-range temporo-AG tracts that belong to the middle longitudinal fascicle (MdLF), whose lateromedial orientation is known to pass superficially to the IFOF at the level of the anterior *stratum sagittale* (Makris et al. 2017; Latini et al. 2020; Di Carlo et al. 2019; Wu et al. 2016b; Bullock et al. 2019).

A last long-range association AG tract was consistently observed with the insula. It includes some projection fibers terminating in the claustrum (Figs. 3 and 10). This AG-Ins tract leaves the angular gyrus by the dorsal pathway and then goes towards the insula at the level of the postcentral gyrus.

Short-range association angular fibers (Figs. 3 and 6 to 9)

We identified a dense network of short-range association AG tracts with the neighboring parietal, occipital and temporal gyri. The closest to the angular gyrus constitute the so-called U-shaped fibers, namely with the supramarginal (SMG), superior parietal (SPG), superior and middle occipital (SOG, MOG), and superior and middle temporal (STG, MTG) gyri (Guevara et al. 2020). Except for SOG, these U-shaped AG fibers were observed in almost all 411 subjects (Suppl. Table 1). Interestingly, these short-range fibers project into the angular gyrus in a tripartite lobar organization (Fig. 9). The short-range parietal terminations are grouped in the superior part of AG along the intraparietal sulcus. The occipital short-range AG tracts project to the posterior part of AG along the anterior occipital sulcus. The short-range temporal terminations are located in the inferior part of AG around the vertical ramus of the superior temporal sulcus. Figure 3 and the 3D-scatter plots in Fig. 9 show in detail that, beyond this tripartite organization, the short-range fiber terminations in AG obey a symmetrical topology depending on the neighboring gyrus in each lobe. The endings of SMG-AG, PoCG-AG, SPG-AG, and PrCu-AG follow an anterior-to-superior distribution in AG similar to the location of the adjacent parietal gyri around AG (Figs. 3 and 6). Following the intergyral parietal nomenclature proposed by Catani et al. (2017), the current AG-SMG corresponds to a parietal angular-to-supramarginal (PAS) tract, AG-PoCG to a parietal inferior-to-postcentral (PIP) tract, and AG-SPG and AG-PrCu to parietal inferior-to-superior (PIS) tracts (Catani et al. 2017). Note that contrary to this previous study, which could not visualize U-shape connections between AG and the precuneus, we consistently observe such U-shape fibers bilaterally in each of the 411 participants and in dissection confirming what was early described in non-human primates (Rozzi et al. 2006). The termination of AG-SOG, AG-MOG, and AG-IOG are distributed in the posterior part of AG in respect to the respective occipital gyri (Figs. 3 and 7) and the termination AG-STG, AG-MTG, and AG-ITG with the respective temporal gyri (Figs. 3 and 8). These short-range parieto-occipital tracts belong to the inferior parietal portion of the vertical occipital fascicle (VOF) (Bullock et al. 2019; Mahdy Ali and Avesani 2021). We observe that these AG fibers of the VOF terminate in the posterior part of AG as initially described (Yeatman et al. 2014).

Projection angular fibers (Figs. 2 and 10)

We identified two types of bilateral projection fibers connecting the angular gyrus (Fig. 2). Cortico-thalamic and cortico-striatal tracts were consistently extracted, running from the angular gyrus through the retro-lenticular portion of the internal capsule to the thalamus and the putamen, respectively. Interestingly, the thalamic fibers enter the thalamus at the level of the pulvinar, while the cortico-striatal fibers terminate in the tail of the putamen (Fig. 10). The second type of angular projection fibers deals with the brainstem and corresponds to cortico-tectal and cortico-pontine fibers (Fig. 2). Both run medio-posteriorly to the cortico-thalamic and cortico-striatal angular tracts.

Commissural angular fibers (Fig. 2)

In addition to the association and projection angular tracts described above, the left and right AG are interconnected via a dense callosal fiber bundle. These homotopic callosal fibers project through the splenium of the corpus callosum to connect the angular gyri bilaterally (Fig. 2).

Discussion

AG, as the postero-dorsal portion of the inferior parietal cortex, together with the supramarginal gyrus (SMG), constitute the so-called Geschwind's territories. These cortical territories, and in particular the AG, were demonstrated critical for different brain functions in both hemispheres as, between others, language (*i.e.*, semantic control and phonological/articulatory encoding), spatial attention and awareness, working memory, calculation, and social cognition (Sarubbo et al. 2015; Zaca et al. 2018; Sarubbo et al. 2016; Thiebaut de Schotten et al. 2005; Seghier 2013). Our macrostructural analysis, integrating multimodal anatomical data provided by high-resolution tractography and microdissection, reveals a highly distributed wiring diagram of WM fibers with AG as a cortical hub. It supports AG's multimodal and pivotal functional roles as an integration area, an epicenter in the sense of (Mesulam 2008), between different sensory inputs (visual, auditory, and somato-sensorial) cortices and the temporal and frontal associative and effector areas.

Considering its sulco-gyral anatomy, AG is split into two parts by the elongation of the superior temporal sulcus within the parietal lobe (Kiriyama et al. 2009). The anterior part of AG faces the temporal border of the posterior third of the superior temporal sulcus (STS), and the posterior one faces the occipital side. Even with possible anatomical variations, we demonstrate that this sulco-gyral structure reflects the first level of short-range connection throughout continuous and homogeneous layers of U-fibers allowing a tripodal inter-lobar connection of AG (Sarubbo et al. 2016) with the superior temporal gyrus (STG), the superior and middle occipital gyri (SOG/MOG), and in the parietal lobe, the supramarginal (SMG) and superior parietal (SPG) gyri (Fig. 9). These local (short-range) cortical connections (involving both Wernicke and Geschwind territories and the convexity of the occipital cortex) play a role in the integration of visual stimuli in the verbal semantic processing and could play a role in the local plasticity phenomena supporting language recovery after restricted damage at the temporo-parieto-occipital junction in the left hemisphere (Sarubbo et al. 2012; Jiao et al. 2020).

Beyond this short-range associative connection, we identified mid- and long-range associative connections, belonging mainly to the SLS but also the ILS (Mandonnet et al. 2018). On the dorsal side, the angular gyrus is predominantly connected with the postcentral gyrus, the precentral gyrus (i.e., the ventral premotor cortex, VPMC), and the posterior portion of the IFG, as part of the classical description of the most ventral portion of the superior longitudinal fascicles, namely SLF-III. It is also strongly connected with the posterior portion of the MFG close to the classical description of the frontal-eyes-field (FEF, for a review (Petit and Pouget 2019)). These connections were also previously demonstrated with the cortico-cortical evoked potentials technique (Matsumoto et al. 2012), highlighting a symmetrical dorso-ventral organization between frontal and parietal cortical territories. In particular, the AG-MFG fibers are part of the classical description of the SLF-II (mid-dorsal component of the SLS, (Vavassori et al. 2021). They constitute the structural background for the known involvement of the dorsal portion of AG facing the intra-parietal sulcus in the fronto-parietal network, crucial for spatial attention and awareness (Thiebaut de Schotten et al. 2005; Sarubbo et al. 2020). This pattern of dorsal connectivity of the AG supports its role in integrating sensory input for motor planning and output. On the ventral side, both tractography and microdissection confirm the existence of a mid- and long-range AG connectivity with the mid-dorsal cortices of the frontal lobe throughout the IFOF (the deepest component of the ILS) (Sarubbo et al. 2013; Caverzasi et al. 2014; Hau et al. 2016; Wu et al. 2016a), and the temporal lobe throughout the superficial and deep components of the posterior transverse system, namely the vertical portion of the SLF and middle longitudinal fascicle (MdLF), respectively (Mahdy Ali and Avesani 2021).

The cross-connection pattern between dorsal and ventral language streams supports the multimodal function role of the AG cortex as revealed by fMRI studies showing functional nodes for semantic and phonological/syntactic elaboration (Vigneau et al. 2006). Different direct electrical stimulation (DES) evidences also demonstrated a high probability of evoking anomia during object naming while deactivating these cortical territories (Sarubbo et al. 2015; Sarubbo et al. 2020), supporting a role of AG in the integration between the semantic elaboration of sensory input and speech encoding. As a matter of fact, in the left hemisphere, this fronto-parietal network (including AG) plays a crucial role in semantic control (Xu et al. 2017).

Our results about AG connections with striatal, thalamic, and brainstem structures support different and growing pieces of evidence coming from neurophysiological and neuroimaging studies. A cortico-striatal circuitry including the cortical territories of the fronto-parietal network (AG-MFG), described above and dedicated to spatial attention, awareness, and the integration of sensory input for motor control (including gait, ocular movements, etc.), was hypothesized since the 1990s on the background of neurophysiological evidence. This cortical-subcortical circuitry includes different deep nuclei and brainstem regions, segregated in direct and indirect pathways (between others, the pulvinar thalami, intralaminar nuclei, mesopontine tegmentum, basal forebrain, globus pallidus, subthalamic nucleus, substantia nigra, and caudate nucleus) (LaBerge 1995; Kinomura et al. 1996). More recently, a functional imbalance (hypo- vs. hyper-activation) between the functional connectivity of certain cortical territories of the fronto-parietal network involved in oculomotor control (notably, the frontal and parietal eyes fields) and the striatal structures (putamen and caudate) was demonstrated as a pathological substrate in Parkinson Disease (Rebelo et al. 2021).

Finally, the bilateral homotopic connectivity between left and right AG reflects the most common pattern of inter-hemispheric connection provided by the corpus callosum (De Benedictis et al. 2016). This pattern of inter-hemispheric connection constitutes the essential structural background for balancing functional activity (*i.e.*, inhibitory/excitatory) between left and right homologous cortices. It was demonstrated that direct current stimulation of the posterior cortices of the IPL, *i.e.*, AG, induced modulation of interhemispheric parietal balance, improving visuospatial attention deficits in neglect patients (Sparing et al. 2009).

To conclude, our combined tractography and microdissection study of the AG wiring diagram reveals its highly distributed connected structure with a central representation between the human brain's main associative layers of WM. The angular gyrus is thus a posterior "angular stone" of associative connections belonging to the mid- and long-range dorsal fibers of the SLS and ventral fibers of the ILS, and short-range fibers, namely U-shaped fibers, and the posterior transverse system, locally connecting all the cortical territories of the temporo-parieto-occipital junction. This dorso-ventral pivotal position reflects the critical role of AG in different networks, particularly in language elaboration and spatial attention and awareness in the left and right hemispheres, respectively. Moreover, we reveal deep nuclei and brainstem connections and a typical inter-hemispheric homotopic connectivity supporting the suggested role, in the context of the fronto-parietal network, in the integration of sensory input for modulating motor control and planning. These structural pieces of evidence all together match with the critical and multimodal functional roles attributed to these cortical territories in both hemispheres on the background of brain mapping data from clinical, neuroimaging, neurophysiological studies.

Declarations

Funding: No particular funding was received for conducting this study.

Conflicts of interest/Competing interests: No conflict of interest for any authors.

Ethics approval :

- The present manuscript is not submitted elsewhere for simultaneous consideration;

- The submitted work is original and has not been published elsewhere in any form or language (partially or in whole);
- No re-use of material to avoid the concerns about text-recycling (self-plagiarism) in the present manuscript;
- The part of the study, including in-vivo diffusion MRI data, was approved by the local ethics committee (CCPRB Basse-Normandie, France).
- The part of the study, including postmortem dissection data, was approved by the Ethical Committee of the Azienda Provinciale per i Servizi Sanitari, Trento, Italy (N° 06/2018).

Consent to participate and for publication: For the part of the study involving *in vivo* diffusion MRI data, all participants gave written consent prior to participation in the study and no opposition to the publication of any type of results generated with their data.

Availability of data and material: The *in vivo* diffusion MRI dataset analyzed in the current study belongs to the BIL&GIN database. The BIL&GIN is not freely available, but a data-sharing model based on collaborative research agreements has been implemented. Request for joint research projects can be made through the BIL&GIN website or by email to the corresponding author of the present paper.

Code availability (software application or custom code): no specific code developed, not applicable.

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Figures

Figure 1

A. Diagram summarizing the main steps of ExTractorflow to filter out false-positive streamlines from a whole-brain tractogram by following brain neuroanatomy organizational principles. In this example, an original tractogram of a single subject initially composed of more than 3.5 million streamlines provides a final whole-brain tractogram of around 590 000 anatomically plausible streamlines once a series of filters (anatomical rules schematically represented with yellow lines) are applied. B. Example of the application of stem/shell fibers extraction. To be considered to belong to a given tract that may connect the angular gyrus (AG) and the middle frontal gyrus (MFG), the anatomically plausible streamlines have to end in AG and MFG and pass through the AG and MFG stems and not through the AG and MFG shells. L: left; R: right; A: anterior; P: posterior

Figure 2

Overview of the different bilateral AG tracts identified in tractography in 411 healthy participants. At the top, short-, mid-, and long-range association tracts connecting AG in the left hemisphere. At the bottom, the homotopic callosal AG fibers and the striatal, thalamic, and brainstem tracts. For illustrative purposes, each represented tract is the concatenation of all the streamlines identified over 411 subjects limited to a maximum of 10 000 streamlines when the total exceeds this value. A: anterior; P: posterior

Figure 3

Schematic overview of the AG connectivity for the short-, mid-, and long-range association fibers (see text for details). In light blue, the fronto-dorsal pathway with the dorsal middle frontal (dMFG), precentral (dPrCG), and inferior (dIFG) gyri. In yellow, the fronto-ventral pathway with the ventral superior frontal (vSFG), middle frontal (vMFG), inferior frontal (vIFG), and fronto-orbital (vFrOrbG) gyri. In orange, the AG connectivity with the insula (Ins). In red, the intra-lobar AG connectivity with the supramarginal (SMG), postcentral (PoCG), and superior parietal (SPG) gyri and the precuneus (PrCu). In dark blue, the short inter-lobar AG connectivity with the superior occipital (SOG), middle occipital (MOG), and inferior occipital (IOG) gyri. In green, the short inter-lobar AG connectivity with the superior temporal (STG), middle temporal (MTG), and inferior temporal (ITG) gyri. Each line corresponds to the centroid of the concatenated WM fibers extracted over the 411 participants for each AG tract. Its diameter represents the averaged diameter of each AG tract estimated with the shape analysis (Suppl. Table 1).

Figure 4

Tractography (top) and dissection (bottom) of the fronto-dorsal AG tracts. For the illustrative purpose of the tractography results, each represented tract is the concatenation of all the streamlines identified over 411 subjects limited to a maximum of 5000 streamlines when the total exceeds this value. A: anterior; P: posterior; S: Superior; I: Inferior; see figure 3 caption for acronyms' labeling.

Figure 5

Tractography (top) and dissection (bottom) of the fronto-ventral AG tracts. See Figure 4 caption for details.

Figure 6

Tractography (top) and dissection (bottom) of the short-range parietal AG tracts. See Figure 4 caption and text for details and acronyms' labeling.

Figure 7

Tractography (top) and dissection (bottom) of the short-range occipital AG tracts. See Figure 4 caption and text for details and acronyms' labeling.

Figure 8

Tractography (top) and dissection (bottom) of the short-range temporal AG tracts. See Figure 4 caption and text for details and acronyms' labeling.

Figure 9

The tripartite lobar organization of AG's mid- and short-range fibers with its neighboring gyri. The short-range parietal terminations (in red) are grouped in the superior part of AG along the intraparietal sulcus. The occipital short-range AG tracts (in dark blue) project to the posterior part of AG along the anterior occipital sulcus. The short-range temporal terminations (in green) are located in the inferior part of AG around the vertical ramus of the superior temporal sulcus. At the bottom, 3D-scatter plots show that, beyond this tripartite organization, the fiber terminations in AG obey a symmetrical topology depending on the neighboring gyrus in each lobe.

Figure 10

Tractography (top) and dissection (bottom) of the association (Insula/Claustrum, left part), and projection AG-Putamen (middle part) and AG-Thalamus (right part) tracts. See Figure 4 caption and text for details and acronyms' labeling.

Supplementary Files

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