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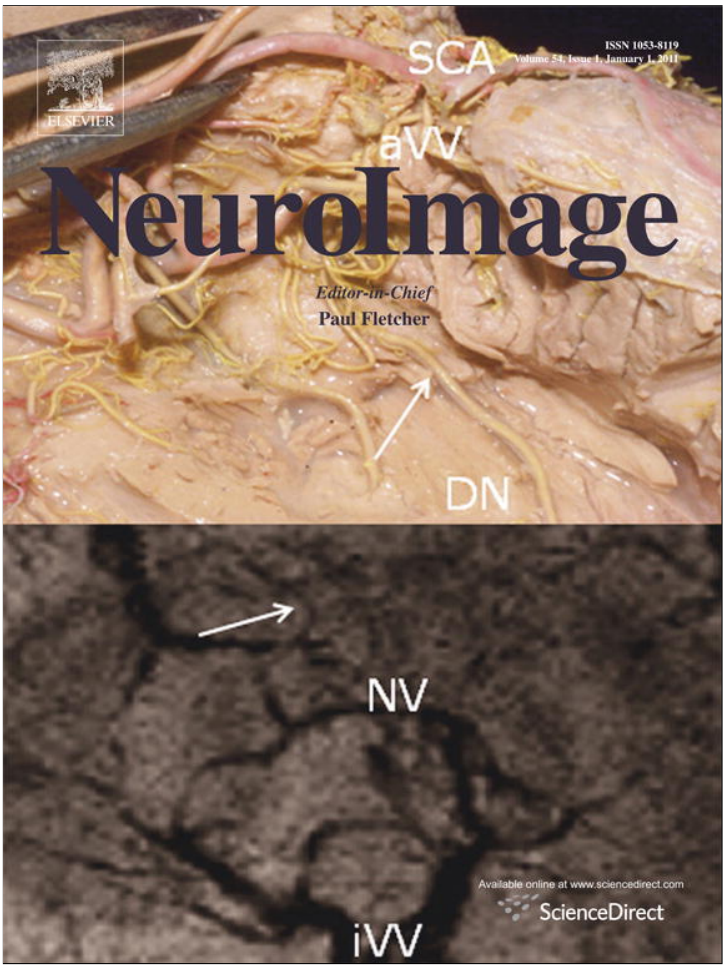

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The variation of function across the human insula mirrors its patterns of structural connectivity: Evidence from in vivo probabilistic tractography

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ABSTRACT

The human insula is a functionally complex yet poorly understood region of the cortex, implicated in a wide range of cognitive, motor, emotion and somatosensory activity. To elucidate the functional role of the insula, the current study used in vivo probabilistic tractography to map the structural connectivity of seven anatomically-defined insular subregions. The connectivity patterns identified reveal two complementary insular networks connected via a dual route architecture, and provide key insights about the neural basis of the numerous functions ascribed to this area. Specifically, anterior-most insular regions were associated with a ventrally-based network involving orbital/inferior frontal and anterior/polar temporal regions, forming part of a key emotional salience and cognitive control network associated with the implementation of goal-directed behavior. The posterior and dorsal-middle insular regions were associated with a network focused on posterior and (to a lesser extent) anterior temporal regions via both dorsal and ventral pathways. This is consistent with the involvement of the insula in sound-to-speech transformations, with an implicated role in the temporal resolution, sequencing, and feedback processes crucial for auditory and motor processing, and the monitoring and adjustment of expressive performance.

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Introduction

Despite increasing interest and exploration into its structure and function, the insula remains an enigmatic and poorly understood region of the cortex. Neuroimaging and lesion studies have identified the insula as a functionally complex region associated with a wide range of verbal and nonverbal activities including speech articulation, auditory processing, cognitive control, somatosensation, multimodal sensory integration, pain perception, interoception, emotional processing, and visceral/gustatory functioning (Craig, 2009; Kurth et al., 2010; Mutschler et al., 2009).

Neural connectivity is heavily implicated in determining the functional specialization of a region, governing the nature and flow of information to and from an area (Behrens and Johansen-Berg, 2005; Plaut, 2002). As such, in an attempt to elucidate its role in these wide ranging and seemingly disparate cognitive tasks, researchers have begun to explore the structural and functional connectivity of the insula. These studies have observed extensive insular interconnection with a widely distributed network of brain regions including the prefrontal and orbitofrontal cortices, temporal regions (particularly the temporal pole), the cingulate gyrus (notably the anterior region), superior and inferior parietal lobules, and subcortical structures including the thalamus and amygdala (Mesulam and Mufson, 1982b; Mufson and Mesulam, 1982). However, due to the invasive nature of traditional techniques for studying connectional architecture, studies of the structural connectivity of the insula have been based almost exclusively on primate models. Researchers have noted that the human insula is larger in size than that found in primates, and have argued that the insula, specifically the anterior portion, may have no true homologue in apes (Craig, 2009; Small, 2010).

Recent studies which have attempted to explore insular connectivity in humans have utilized non-invasive resting-state functional connectivity measures to identify functional neural networks involving the insula and other areas of the brain (Cauda et al., 2011; Deen et al., 2011). These studies have identified a number of dissociated functional networks involving many of the cortical regions identified by primate models, suggesting an underlying structural connectivity to the observed functional connections (van den Heuvel et al., 2009). However, while studies have found strong relationships between functional and structural connectivity in other regions, this is not always the case, and researchers have noted that the functional–structural connectivity relationship between these two methodologies may not be a simple one-to-one mapping (e.g., Damoiseaux and Greicius, 2009; Uddin et al., 2008; Zhang et al., 2010).

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The advent of modern diffusion neuroimaging and probabilistic tractography has now made possible the investigation of structural connectivity in the human brain in vivo (Parker et al., 2003). Recent studies have provided initial explorations into the delineation of white matter pathways of the human insula via tractography (e.g., Baliki et al., 2009; Fernandez-Miranda et al., 2008; Kalani et al., 2009). However, a systematic exploration of the neural connectivity of anatomically-based insular subdivisions has yet to be conducted. The current study used probabilistic tractography to map the white matter pathways of seven anatomically-defined regions of the human insula. Such mapping will help to elucidate the role of the structural connectivity in the myriad of functions ascribed to the insula.

Materials and methods

Participants and image acquisition

Twenty-four participants (11 females; mean age = 25.9, range = 19–47) gave written informed consent to participate in the study, which was approved by the local ethics boards. All participants were right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971).

Imaging data were acquired on a 3T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands), using an 8 element SENSE head coil. Diffusion weighted imaging was performed using a pulsed gradient spin echo echo-planar sequence with TE = 59 ms, TR ≈ 1500 ms (cardiac gated), G = 62 mTm^{-1}, half scan factor = 0.679, 112 × 112 image matrix reconstructed to 128 × 128 using zero padding, reconstructed resolution 1.875 × 1.875 mm, slice thickness 2.1 mm, 60 contiguous slices, 61 non-collinear diffusion sensitization directions at $b = 1200\ smm^{-2}$ ($\Delta = 29.8$ ms, $\delta = 13.1$ ms), 1 at $b = 0$, and SENSE acceleration factor = 2.5. For each diffusion gradient direction, two separate volumes were obtained with opposite directional *k*-space traversal (and thus reversed phase and frequency encode direction), with phase encoding in the left–right/right–left direction in order to reduce signal distortion (Embleton et al., 2010). Acquisitions were cardiac gated using a peripheral pulse unit positioned over the participant's index finger (n = 10), or an electrocardiograph (n = 3). The diffusion weighted images were corrected for susceptibility- and eddy current-induced distortion using the method described in Embleton et al. (2010). A co-localized T_2-weighted turbo spin echo scan, with in-plane resolution of 0.94 × 0.94 mm and slice thickness 2.1 mm, was obtained as a structural reference scan to provide a qualitative indication of distortion correction accuracy. A high resolution T_1-weighted 3D turbo field echo inversion recovery scan (TR ≈ 2000 ms, TE = 3.9 ms, TI = 1150 ms, flip angle 8°, 256 × 205 matrix reconstructed to 256 × 256, reconstructed resolution 0.938 × 0.938 mm, slice thickness 0.9 mm, 160 slices, SENSE factor = 2.5), was also acquired for the purpose of high-precision anatomical localization of seed regions for tracking.

Definition of regions of interest

Anatomically, the insula is comprised of two main subdivisions separated by a central insular sulcus: an anterior portion, composed of three (anterior, middle, and posterior) short gyri which converge ventrally at the insular apex (the most laterally projecting area); and a posterior portion, composed of two (anterior and posterior) long gyri, which converge ventrally to form the posterior pole (Naidich et al., 2004). Cytoarchitectonically, the insula has traditionally been found in both humans and primates to be composed of three distinct regions: a ventral-anterior agranular region, a dorsal-posterior granular region, and an intermediary dysgranular transition region (Mesulam and Mufson, 1982a). Previous anatomical and functional connectivity studies in both primates and humans have identified differences in insular connectivity along both the anterior–posterior and dorsal–ventral planes, consistent with the (micro-) structural organization of the insula (Cauda et al., 2011; Deen et al., 2011; Mesulam and Mufson, 1982a; Mufson and Mesulam, 1982). To explore any possible topographic or cytoarchitectonic differences in insular connectivity between the anterior–posterior and dorsal–ventral regions, seven anatomically-defined regions of interest (ROIs) were identified for white matter tractography in each hemisphere (see Fig. 1): one placed in the dorsal-most point of each insular gyrus (anterior: anterior short (Aasg), middle short (Amsg), posterior short (Apsg); posterior: anterior long (Palg), posterior

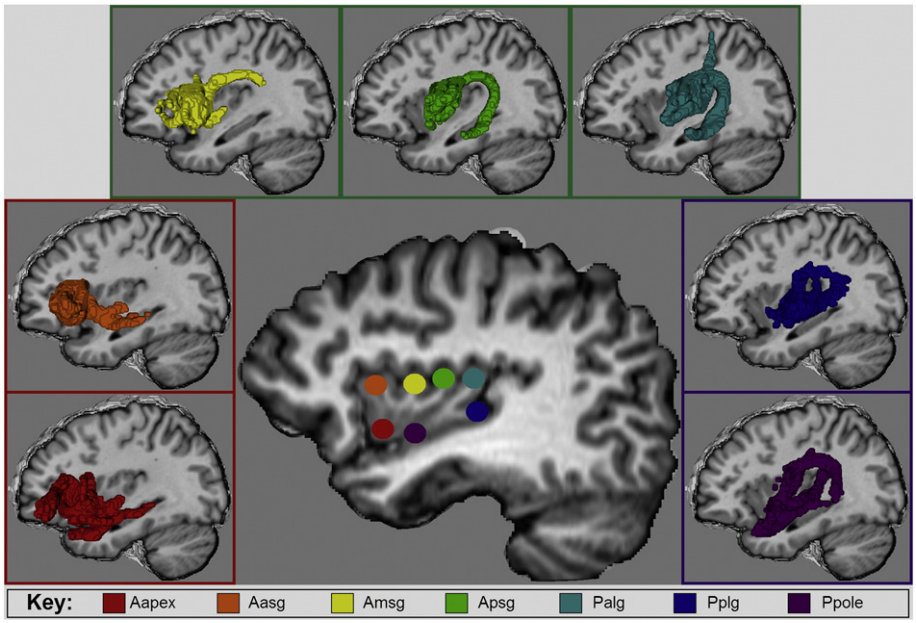

Fig. 1. Location of the seven insular areas used as seed regions for probabilistic tracking (center), and examples of fiber pathways found for each tractographic region in the anterior (left), posterior (right), and transitional (top) networks derived from current tracking results. Abbreviations: Aapex = anterior apex (red), Aasg = anterior anterior short gyrus (orange), Amsg = anterior middle short gyrus (yellow), Apsg = anterior posterior short gyrus (green), Palg = posterior anterior long gyrus (teal), Pplg = posterior posterior long gyrus (blue), Ppole = posterior pole (purple).

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long (Pplg)); and a further two in anterior and posterior ventral regions, in the anterior apex (Aapex) and posterior pole (Ppole).

ROIs were identified and defined in each hemisphere based on topographic descriptions and boundaries outlined in previous anatomical and MRI studies (Afif et al., 2009; Cohen et al., 2010; Naidich et al., 2004; Tanriover et al., 2004; Ture et al., 1999), and drawn manually for each participant on the high-resolution T_1-weighted scan. The insula was first located using the sagittal view, and the dorsal (superior limiting sulcus), ventral (inferior limiting sulcus and limen insulae), and medial (extreme capsule) boundaries identified, as well as the anterior commissure–posterior commissure (AC–PC) line (identified on the midline sagittal slice). Each ROI was then identified and its limits defined on both axial and sagittal slices. For each of the five gyral ROIs, the insula was traced on the axial view from each gyri's dorsal limit down approximately one-third of their length. This was above the line of the AC–PC in most instances, except for the Pplg, where this cut the line of the AC–PC in a number of participants. The Aapex was identified as the lateral-most ventral point below the line of the AC–PC. The Ppole was identified as the junction of the Aalg and Pplg below the AC–PC line and above and posterior to the limen insulae. For all ROIs, particular attention was paid to the medial boundary with the extreme capsule. To ensure accuracy, all ROIs were initially drawn on the axial view, refined on the sagittal view, and finally checked and modified if necessary on the coronal view.

Fiber tracking and anatomical localization of fiber pathways

Unconstrained probabilistic tractography was performed with a dedicated software package using the PICo method, sampling the orientation of probability density functions (PDFs), generated using the constrained spherical deconvolution method (Parker et al., 2003; Tournier et al., 2008). The current study utilized a probabilistic as opposed to deterministic tractography approach due to the increased capability of the former to deal with the branching of white matter tracts, and its ability to provide a measure of the uncertainty of the reconstructed pathways (Jones, 2008). Probabilistic methods have also been found to be more robust when dealing with uncertainty in the distribution of fiber orientations (Descoteaux et al., 2009). However, intrinsic limitations are inherent in all tractographic approaches. Given that the output of probabilistic algorithms is a quantification of the probability that a pathway exists between the seed and a given voxel, it cannot define connections unambiguously, and can thus suffer from both Type I and Type II errors, especially when examining connectivity between distant regions (Jones, 2008; Parker and Alexander, 2003). The reader is referred to the Discussion for a more detailed coverage of these issues.

In the current study, 20 000 streamlines were initiated from each voxel within an ROI. Step size was set to 0.50 mm. Stopping criteria for the streamlines were set so that tracking terminated if pathway curvature over a voxel was greater than 180°, or the streamline reached a physical path limit of 500 mm.

To allow for anatomical localization and inter-subject comparisons, the tracking results for each participant were spatially normalized into MNI template space using the DARTEL toolbox supplied as part of SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm; Ashburner, 2007). The cortical brain regions associated with each fiber pathway were determined using brain region masks from the AAL atlas, generated using the WFU Pick Atlas (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). Due to the large size of the brain masks, and interest in potential functional differences between identified sub-regions within these areas, the AAL masks for the superior, middle, and inferior temporal gyri were subdivided into rostral (anterior) and caudal (posterior) subdivisions, which were defined by a vertical division lying perpendicular to the AC–PC plane, which bisected the brain at approximately the midway point between the AC and PC. For each ROI, the AAL masks were overlaid over each participant's spatially normalized tracking data, and a maximum connectivity value (ranging from zero to 20 000), between the seed region and each area of the brain was obtained.

The resultant streamline-based connectivity matrices were subjected to a double threshold to ensure that only connections with a high probability in the majority of participants were considered. At the first-level individual threshold, for each participant, the maximum connectivity values across all ROIs and AAL brain regions were used to determine the distribution of connection values between the insula and all other areas of the brain. The λ-value of the Poisson distribution identified was then used to determine a threshold value at $p = .05$, above which a connection between an ROI and brain region was deemed to exist with a high degree of probability. At the second-level group stage, from the set of individual, high-probability connections, we selected only those that were consistently identified across participants. We used both a stringent (≥75% of participants, i.e., at least 18/24 participants), and more relaxed (≥50% of participants, i.e., at least 12/24 participants) criteria for consistency across participants.

Results

The connectivity profile and connectivity fingerprints for each insula ROI are presented in Table 1 and Fig. 2. Examples of the associated fiber tracts are projected onto the brain in Fig. 1, with comparative examples between the left and right hemispheres presented in Fig. 2. As can be seen from Table 1 and Fig. 2, insular connectivity was very similar for both the left and right hemispheres, with some small exceptions. Examination of the insular connectivity patterns and associated fiber pathways reveals three insular subdivisions: 1) an anterior region involving Aapex and Aasg; 2) a posterior region involving Pplg and Ppole; and 3) a graduated intermediary transitional region involving Amsg, Apsg and Palg.

The pattern of connectivity for each of the three insular areas can be summarized as follows (Fig. 1). The anterior insular regions (Aapex and Aasg) showed strong frontal connectivity to orbitofrontal and inferior frontal (triangular and opercular) regions, as well as connections with several anterior temporal areas and the posterior middle temporal gyrus. Connectivity was exclusively via a ventral pathway. While great caution must be taken in attempting to identify specific anatomical tracts from tracking results, particularly in the differentiation of tracts which follow a similar course and are bundled together, at least some inferences can be made. Previous tract tracing and dissection studies in both monkeys and humans have identified three ventral pathways which course between frontal and temporal areas, passing underneath the insula on their trajectories: the uncinate fasciculus (UF), which connects temporopolar areas to orbital and medial prefrontal cortices; the extreme capsule fiber system (EC), positioned behind the UF, which connects superior and middle temporal regions along their extent to inferior frontal areas (particularly pars triangularis and the frontal operculum), and which contains along its length many short association fibers between the insula and frontal/temporal opercula; and the inferior occipito-frontal fasciculus (IFOF), situated superior to the UF, which connects the orbitofrontal and occipital cortices, coursing medially and rostrally along the length of the middle temporal gyrus, ventral to the EC (Fernandez-Miranda et al., 2008; Kier et al., 2004; Martino et al., 2010; Schmahmann et al., 2007). The current tractography results for the anterior insular ROIs are consistent with the trajectories of all three pathways, although only Aapex was revealed to have underlying connections via the UF (Figs. 1 and 3). The connectivity along the IFOF did not appear to fully reach the occipital region, terminating in most participants at the posterior middle temporal gyrus, which may reflect the apparent bifurcation of the IFOF at this point into parietal and occipital termination pathways (Martino et al., 2010).

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Table 1
Connectivity profile for each insular region in both the left and right hemispheres.

	Left hemisphere							Right hemisphere						
	Anterior		Transitional			Posterior		Anterior		Transitional			Posterior	
	Aapex	Aasg	Amsg	Apsg	Palg	Pplg	Ppole	Aapex	Aasg	Amsg	Apsg	Palg	Pplg	Ppole
Frontal middle orbital	1							1						
Frontal inferior operculum		**1**	**1**	**1**	1				**1**	**1**	**1**			
Frontal inferior triangular	**1**	**1**	**1**					**1**	**1**	**1**				
Frontal inferior orbital	**1**	**1**	**1**					**1**	**1**					1
Postcentral				1	**1**							**1**		
Rolandic operculum			**1**	**1**	**1**	**1**				**1**	**1**	**1**	1	
Parietal inferior supramarginal					**1**							**1**		
Temporal inferior posterior								1						
Temporal middle anterior	**1**	1					**1**	**1**						**1**
Temporal middle posterior	**1**	1		1	1	**1**	**1**	1	1				**1**	**1**
Temporal superior anterior	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		1	**1**	**1**	**1**	**1**
Temporal superior posterior				1	**1**	**1**	**1**	**1**	1	1	**1**	**1**	**1**	**1**
Temporal pole superior	**1**						**1**	**1**		1			1	**1**
Temporal pole middle	1													
Heschl				1	**1**	**1**	1				**1**	**1**	**1**	
Occipital middle													1	
Putamen	1	1	1		1	**1**	**1**	**1**	**1**	**1**	1	**1**	**1**	**1**
Aapex	–	**1**	**1**				**1**	–	**1**	1				1
Aasg	**1**	–	1					1	–	**1**				
Amsg	1	**1**	–	**1**					**1**	–	**1**			
Apsg			**1**	–	**1**					**1**	–	**1**		
Palg				**1**	–	**1**					**1**	–	1	
Pplg					**1**	–	**1**					1	–	**1**
Ppole	**1**	1				**1**	–	**1**					**1**	–

NB: Numbers in bold represent a strict consistency criteria of over 75% of participants (i.e., at least 18/24 participants), while numbers not in bold represent a relaxed consistency criteria of over 50% of participants (i.e., at least 12/24 participants).

In contrast to the anterior regions, the focus of connectivity for the posterior insular regions (Pplg and Ppole) was predominant with posterior superior and middle temporal areas including Heschl's gyrus, with additional connectivity observed with the anterior superior temporal gyrus. Pplg also demonstrated connections to the rolandic operculum. Examination of the underlying fiber pathways of the posterior insula reveals connectivity via both a dorsal and ventral route. Ventrally, the insula–temporal connections appear to correspond to the fibers of the EC and possibly the middle longitudinal fasciculus (MdLF), whose fibers travel the length of the superior temporal gyrus, and split rostrally to terminate in the temporal pole or join the fibers of the EC (Schmahmann et al., 2007). Like Aapex, Ppole was found to have additional connectivity with the temporal pole. However, while Aapex appeared to connect to the temporopolar region via the UF, the connective pathway of Ppole appeared to be via the EC and/or MdLF (Fig. 3). Based on its trajectory, the dorsal route appears to most closely align with the known pathway of the arcuate fasciculus (AF), traveling above the superior limiting sulcus of the insula and arching around the sylvian fissure to terminate in the posterior temporal region (Makris et al., 2005). However, the trajectory of the posterior insula projections appears to be focused caudally, with a lack of connections along the AF's dorsal segment to frontal areas.

The transitional insular area (Amsg, Apsg, and Palg) demonstrated a graduated pattern of hybrid connectivity to frontal and temporal regions, as well as connections with the rolandic operculum and the postcentral gyrus. Palg demonstrated additional connectivity with the supramarginal gyrus. An examination of the fiber pathways involved reveals predominantly dorsal connections which, like the posterior insula dorsal pathway, appear consistent with the known trajectory of the AF. Additional short association fibers connect the transitional areas with the anterior superior temporal gyrus, most likely involving fibers of the EC. Consistent with its position on the border with the ventrally-connected anterior region, Amsg demonstrated greater ventral connectivity with inferior frontal regions via this EC pathway.

In relation to the observed within-insula connectivity, anterior and posterior regions showed strong within-subregion connectivity, while anterior–posterior interconnectivity was found in the transitional area (particularly between Apsg and Palg), as well as between the ventrally-located ROIs (Aapex and Ppole; Table 1).

Discussion

The current in vivo tractography study of the structural connectivity of the human insula revealed two complementary neural networks connected via a dual route architecture: 1) an anterior network connecting anterior-most insular areas (Aapex, Aasg) with orbital/inferior frontal and temporal regions via an exclusively ventral pathway involving fiber tracts including the UF, EC, and IFOF; and 2) a posterior network involving connectivity between the posterior-most insular areas (Pplg, Ppole) and predominantly posterior (and to a lesser extent, anterior) temporal regions via dorsal and ventral pathways involving the EC and AF. A transitional area (Amsg, Apsg, Palg) involving the dorsal-middle region of the insula was also found which demonstrated a graduated pattern of anterior–posterior hybrid connectivity between frontal and temporal areas. This differentiation of the insula into anterior, posterior, and transitional subdivisions is consistent with previous anatomical and functional parcellations in both primates and humans (Cauda et al., 2011; Deen et al., 2011; Mesulam and Mufson, 1982a). In addition, the connectivity profile of the insula found in the current study corresponds well with previous primate studies which have also identified strong patterns of structural connectivity between the insula and regions including the orbital cortex, inferior frontal gyrus, temporal pole, superior temporal cortex, primary auditory cortex, and areas adjoining the motor and somatosensory cortices (Mesulam and Mufson, 1982b; Mufson and Mesulam, 1982). The strong frontal connectivity found for anterior but not posterior divisions of the insula is also consistent with previous animal studies which have shown the posterior insula to contain fewer frontal projections than other insular regions (Mufson and Mesulam, 1982). It is interesting to note that the rostrocaudal gradient of

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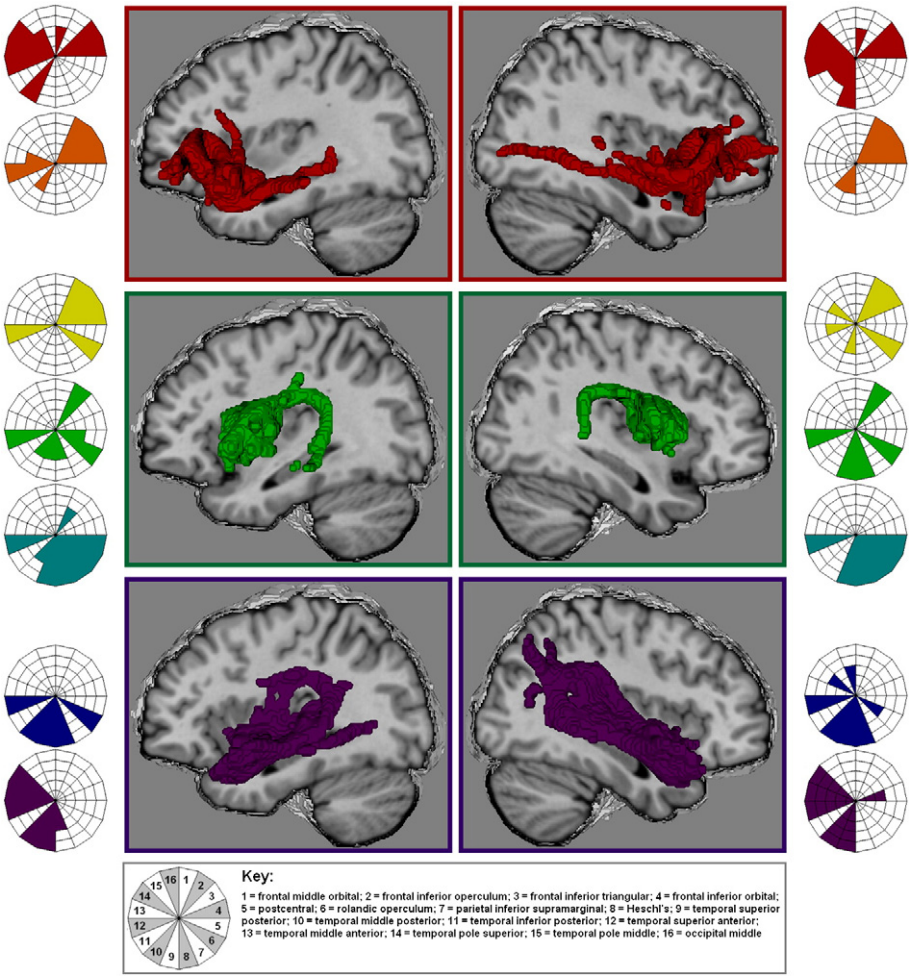

Fig. 2. Comparison of connectivity results between the left and right hemispheres (presented on the left and right sides of the figure, respectively). Central figures depict comparative examples of representative fiber pathways in the anterior (Aapex; top), transitional (Apsg; middle), and posterior (Ppole; bottom) networks. Outer figures represent binary cortical–cortical connectivity fingerprints for each of the seven insular ROIs, based on the connectivity profiles presented in Table 1. Wedges filled to the outer edge represent brain regions demonstrating connectivity with the respective insula ROI using a strict consistency criterion of 75% of participants, while half-filled wedges represent a relaxed consistency criterion of 50% of participants. For color coding of connectivity fingerprints see Fig. 1.

connectivity and brain networks identified in the current study are strongly mirrored by a very recent tractographic study which utilized probabilistic tractography to explore the variations in neural connectivity patterns across the insula (Cerliani et al., in press).

Recent studies which have attempted to explore insular connectivity in humans have predominantly utilized non-invasive resting-state functional connectivity measures (Cauda et al., 2011; Deen et al., 2011). These studies have identified a number of dissociated insular networks involving many of the cortical regions found in the current tractographic study. However, these functionally-based networks have consistently been associated with a far greater and more widely distributed network of insular interconnectivity, involving a number of insula–cortical connections not observed in the current study, most notably between the anterior insula and anterior cingulate cortex (ACC; Cauda et al., 2011; Medford and Critchley, 2010; Taylor et al., 2009). It is interesting to note that in contrast to the consistency with which anterior insula–ACC functional correlations have been identified by resting-state measures, white matter connections between the two areas in the human brain have been only inconsistently observed via tractographic methods, if at all (Beckman et al., 2009; van den Heuvel et al., 2009). Indeed, a very recent study which utilized a probabilistic tractography approach similar to that used in the current study also failed to demonstrate any evidence for direct insula–ACC connectivity (Cerliani et al., in press). As noted previously, functional connectivity does not necessarily infer structural connectivity, and studies have observed functional connections between regions where no structural connectivity exists (Damoiseaux and Greicius, 2009; Uddin et al., 2008; Zhang et al., 2010). It has been hypothesized that these functional correlations most likely result from indirect structural connections via shared brain regions (Damoiseaux and Greicius, 2009). As such, it is highly possible that functional correlations between the insula and other cortical regions such as the ACC may not be the result of direct neural connections between these areas, but may instead be the result of mediation via a third cortical area. However, there is some evidence from primate tracer studies that direct insula–ACC anatomical connections may indeed exist. These studies have consistently demonstrated the existence of both afferent and efferent direct anatomical fiber pathways between the insula and ACC, although with only light to moderate labeling observed (Mesulam and Mufson, 1982b; Mufson and Mesulam, 1982). As such, it is also possible that the functional connectivity observed between the two regions does indeed reflect the existence of an anatomical connection in humans, but that the probabilistic tractography techniques used in this and previous studies are not currently capable of identifying these pathways. Whether the failure to find insula–ACC structural connectivity in humans via tractographic methods is a true reflection of the absence of any direct anatomical pathways between the two regions,

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or the result of methodological limitations, is an issue yet to be resolved.

As noted in the Introduction, previous functional imaging studies have implicated the insula in a wide range of cognitive skills including emotional salience, cognitive control, language processing, and motor functioning (Kurth et al., 2010; Mutschler et al., 2009). Although there may be important, additional connective pathways left undetected in the current study, the differences in connectional architecture found between the anterior and posterior insular regions, and the identification of underlying dorsal and ventral neural pathways, provide important insights into the functional role of this highly complex area.

First looking at the anterior-most portion of the insula, previous studies have implicated the anterior insula in a range of cognitive processes including pain perception, disgust, affiliative emotional states, attention and arousal, and the initiation and maintenance of task set behavior (Caruana et al., 2011; Dosenbach et al., 2006, 2007; Eckert et al., 2009; Jabbi et al., 2008). To account for its involvement across these tasks, it has been argued that the anterior insula forms part of a saliency network which plays a key role in the implementation of goal-directed behavior, ascribing emotional significance to perceived stimuli, controlling arousal and attention, and integrating information into decision making processes to guide behavioral responses (Dosenbach et al., 2006, 2007; Menon and Uddin, 2010; Seeley et al., 2007; Weich et al., 2010). The current tractography results appear to support this functional hypothesis, with the anterior insula (Aapex, Aasg) forming a ventrally-based network with orbitofrontal and temporopolar regions, by which semantic information (from the temporal pole) and emotional content and valence information (from paralimbic and subcortical structures) may converge. The finding of the involvement of the UF in the connective pathways underlying this network is also consistent with this functional interpretation, with previous studies characterizing this fiber tract as a limbic association pathway critical for processing the emotional content of stimuli and the regulation of emotional responses (Schmahmann et al., 2007).

In addition to the orbitofrontal and temporopolar areas, the anterior insula was also observed to have a strong connectivity with the ventrolateral prefrontal cortex (VLPFC). Due to the prominence of the VLPFC in language, this connective pathway has often been interpreted as evidence for the involvement of the anterior insula in language functioning, notably articulation (Cerliani et al., in press). Indeed, a role for the insula in language is also suggested by the current tractographic results (see below). However, in addition to linguistic processing, the VLPFC has also been strongly implicated in a range of cognitive control functions, including the detection of behaviorally relevant stimuli in the environment, the maintenance of stimulus information, and behavioral and affective self-control (Cohen et al., in press; Levy and Wagner, 2011; O'Reilly, 2010). As such, the connectivity observed between the anterior insula and VLPFC in the current study may be a further indication of the involvement of these regions in emotional saliency and cognitive control processes, allowing for the integration of affective and environmental information, and the regulation and control of emotional response.

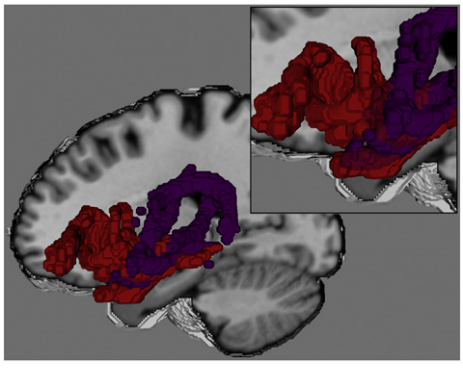

Fig. 3. Comparison of temporopolar connections associated with Aapex (red) and Ppole (purple). Aapex demonstrates connectivity between orbitofrontal regions and the temporal pole via the uncinate fasciculus (UF), while Ppole demonstrates connectivity between posterior and polar temporal areas via the extreme capsule (EC) and/or the middle longitudinal fasciculus (MdLF).

The posterior-most insular region (Pplg, Ppole) was found to form a network with predominantly posterior temporal areas including the auditory cortex, while transitional insular areas (Amsg, Apsg, Palg) demonstrated a similar pattern but with additional connectivity to regions underlying the motor and somatosensory cortices. The patterns of connectivity found for these insular regions, and the involvement of the AF and EC fiber pathways, appear consistent with the involvement of these areas in aspects of language functioning. The role of the insula in language has been widely debated, however, a number of studies have implicated the insula in a number of linguistic tasks including speech production (particularly articulation), singing, and auditory speech processing (Bamiou et al., 2003, 2006; Dronkers, 1996; Eickhoff et al., 2009; Riecker et al., 2000; Wise et al., 1999). The current tractography results support these findings, and suggest a role of the posterior and middle-dorsal insula in a 'repetition-phonological' network involved in the mapping of auditory information onto motor action, necessary for the sound-to-speech transformations underlying repetition. Within this repetition network, posterior temporal regions have been associated with the transient representation of the phonetic sound sequences to be repeated (Scott et al., 2000; Wise et al., 2001), while the insula (along with other cortical motor regions) has been associated with the translation of this phonetic information into vocal tract motor patterns for articulation (Eickhoff et al., 2009; Price, 2010). The current study found no direct connections between the insula and motor areas of the brain, however, connections were observed with the rolandic operculum which underlies the primary and secondary motor areas, as well as the putamen which has also been heavily implicated in the planning and execution of complex motor movements (Alexander and Crutcher, 1990; Deffains et al., 2010). The language-related functions of the insula in this repetition network and its involvement in sound-to-speech transformations may follow from a more general role in temporal resolution and sequencing processes, crucial for both auditory and motor processing (Bamiou et al., 2006; Bengtsson et al., 2004; Berlin and Zatorre, 2000; Colativa and Weisberg, 1978; Weiller et al., 2011). Alternatively, it may constitute an extension of the insula's role in the control of goal-directed behavior, using auditory–motor feedforward and feedback loops to monitor and adjust performance (Dosenbach et al., 2006; Houde and Jordan, 1998; Mutschler et al., 2009). Additionally, it has often been noted that within language production, linguistic information needs to be integrated with affective prosodic information in order to convey the appropriate emotional content of the message (Ackermann and Riecker, 2004; Riecker et al., 2000). The dorsal-middle and posterior insula may act to integrate emotional information from the anterior insula with articulatory processes in order to convey appropriate emotional intonation in speech.

Finally, the identification of complementary dorsal and ventral insular pathways found in the current study contributes to our increasing understanding of the importance of the dual-route architecture in the human brain. A dual-route neural network organization, involving dorsal and ventral processing streams, has been found for an increasing number of cognitive processes including vision (Mishkin et al., 1983), language (Parker et al., 2005; Weiller et al., 2011), and attention (Umarova et al., 2010). Researchers have associated the dorsal ("where") route with processes involving the analysis of sequences, sensorimotor mapping, and sensory feedback, while the ventral ("what") route has been ascribed functions associated with the mapping of information onto conceptual representations, the selection of salient features for meaning, and the integration of conscious perception

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with the relevance of a stimuli to the self (Weiller et al., 2011). These ascribed processes have strong parallels with the current interpretation of the functional roles associated with the insula, and suggests that this dual-route structural–functional organization may be crucial for the performance of higher cognitive functions throughout the brain. At a more general level, the dual pathway architecture identified in the current study can be seen to form an anatomical and functional frontal-temporal processing 'loop'. The insula, with its position at the center of this loop and its strong interconnectivity with the pathways involved, seems ideally situated to act as a key hub for the communication and integration of information within this network.

Limitations of the current study

The current study utilized in vivo probabilistic tractography to explore the neural connectivity and associated fiber tracts of the human insula, and identified a number of pathways which were consistent with previous primate tracer and human anatomical dissection studies. However, while the probabilistic tractography approach can successfully delineate white matter fiber pathways in the brain, even in regions of high anatomical complexity (Parker and Alexander, 2003, 2005), important limitations remain which must be acknowledged and considered when interpreting any tractography results. The key limitations of relevance to the current study relate to the issues of distance effects and thresholding (Jones, 2008; Morris et al., 2008).

In any tractographic technique, a degree of uncertainty in fiber orientation is present at each step in the propagation of a pathway. This accumulation of uncertainty from voxel to voxel as the streamline is advanced results in a decrease in connection probability with increasing path length, and a progressive dispersion of the streamlines with distance from the seed (Morris et al., 2008). As a result, long distance connections are more difficult to identify and are associated with lower probability values. This not only leads to difficulty in tracking long-range connections but also in the interpretation of any tracking results, as the probability of connection is not uniform across distance. As a result, it is difficult to determine a threshold value which will successfully identify true positives while simultaneously minimizing the rate of both Type I errors in regions close to the seed and Type II errors in more distant regions. In the current study, a threshold value was determined by taking the average of the insular connectivity distribution across the entire brain, reflecting values from regions with both short and long connectivity distances. This procedure most likely produced a conservative cut-off value for longer pathways and may have resulted in a number of false negatives for the long-range connections. Thus, it is important to acknowledge that there may be long-range connections left undetected in the current study. However, as one of the key aims of this (and any other) tractography study is to identify those tracts most likely to be present in the human brain with a high degree of probability, it is believed that the high cut-off value used would likely have produced fewer false positives in the long range connections and fiber pathways identified.

A further problem associated with the issue of threshold definition (for both tracking results and the definition of consistency across participants) relates to the current lack of any empirically supported standard methodology or criterion for determining these values. This has resulted in a relative degree of arbitrariness in threshold selection (and lack of consistency across studies), with researchers selecting values which appear sound but which often have minimal underlying methodological or statistical justification or validation. The current study attempted to introduce a degree of objectivity into tract threshold determination by analyzing the distribution of connection values between the insula and the rest of the brain, and utilizing probabilistic cut-off values associated with the identified distributions. Across-participant consistency was determined by utilizing 50% (relaxed) and 75% (stringent) threshold criterion. While these specific values can be viewed as somewhat arbitrary in their selection, they are successful in thresholding the results to include only those connections consistently observed across most participants in the study, and similar values have been used in previous studies (e.g., Cerliani et al., in press). The goal of thresholding is to identify those connections which are likely to exist with a high degree of probability and which appear to reflect the underlying structural and functional organization of the brain across the population (while allowing for a degree of intersubject variability, inherent in all studies of the human brain). While it is acknowledged that a degree of subjectivity in threshold selection still remains, the threshold approach used in the current study goes some way to achieving these aims.

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