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La connectivité structurelle de l'insula chez l'humain

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Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de maîtrise ès sciences (M.Sc.)
en sciences neurologiques

Août, 2016

Résumé

L'insula est une structure complexe impliquée dans une variété de fonctions. Les études de connectivité par traçage chez les primates non humains ont révélé une multitude de connexions corticales entre l'insula et les lobes frontal (cortex orbitofrontal, cortex préfrontal, régions cingulaires, aire motrice supplémentaire), pariétal (cortex somatosensoriel primaire et secondaire) et temporal (pôle temporal, cortex auditif, cortex prorhinal et entorhinal). Les études de tractographie chez l'humain ont révélé des connexions structurelles similaires, mais n'ont pas rapporté de connexion avec le cortex cingulaire, malgré que cette structure soit reconnue comme étant fonctionnellement connectée à l'insula. Ce projet vise à approfondir la recherche sur la connectivité structurelle entre ces deux structures ainsi que d'autres régions connues comme étant fonctionnellement connectées à l'insula, à l'aide d'un échantillon plus grand et des plus récentes méthodes en tractographie par l'imagerie à haute résolution de diffusion angulaire basée sur des a priori anatomiques.

En analysant les données de 46 participants adultes en bonne santé, notre étude rapporte un large éventail de connexions entre l'insula et les lobes frontal, temporal, pariétal et occipital ainsi que les régions limbiques, suivant un patron d'organisation rostrocaudal. Notamment, nous démontrons pour la première fois une connexion structurelle claire entre l'insula et les gyri cingulaire, parahippocampique, supramarginal et angulaire ainsi que le précunéus et les régions occipitales.

Mots-clés : insula, insulaire, diffusion, tractographie, connectivité

Abstract

The insula is a complex structure involved in a wide range of functions. Tracing studies on non-human primates reveal a wide array of cortical connections in the frontal (orbitofrontal and prefrontal cortices, cingulate areas, and supplementary motor area), parietal (primary and secondary somatosensory cortices) and temporal (temporal pole, auditory, prorhinal and entorhinal cortices) lobes. However, recent human tractography studies have not observed connections between the insula and the cingulate cortices, although these structures are thought to be functionally intimately connected. In this work, we try to unravel the structural connectivity between these regions and other known functionally connected structures, benefiting from a higher number of subjects and the latest state-of-the-art high angular resolution diffusion imaging (HARDI) tractography algorithms with anatomical priors.

By performing a HARDI tractography analysis on 46 young normal adults, our study reveals a wide array of connections between the insula and the frontal, temporal, parietal and occipital lobes as well as limbic regions, with a rostro-caudal organization in line with tracing studies in macaques. Notably, we reveal for the first time in humans a clear structural connectivity between the insula and the cingulate, parahippocampal, supramarginal and angular gyri as well as the precuneus and occipital regions.

Keywords: insula, insular, diffusion, tractography, connectivity

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Liste des abréviations

AB	Aire de Brodmann
IHRDA (HARDI)	Imagerie à haute résolution de diffusion angulaire
IRMf	Imagerie par résonance magnétique fonctionnelle
IRMfer	Imagerie par résonance magnétique fonctionnelle à l'état de repos
ISD (DSI)	Imagerie du Spectre de Diffusion
ITD (DTI)	Imagerie par tenseur de diffusion
MNI	Montreal Neurological Institute
SVCD (BOLD)	Séquence sensible aux variations de concentration en désoxyhémoglobine

Remerciements

J'aimerais manifester ma gratitude à l'égard de mon superviseur, Dr Dang K. Nguyen, pour avoir accepté de me diriger, pour son inconditionnel soutien et surtout, pour sa patience. Mon cosuperviseur, Pr Pierre Rainville, et les membres de mon comité de maîtrise, Pr Franco Lepore et Pr Isabelle Rouleau, pour leurs support, confiance et encouragements. Je voudrais également remercier le directeur des programmes d'études supérieures du département de neurosciences, Pr Richard Robitaille, pour son appui académique.

Un grand merci au Pr Maxime Descôteaux, à Jean-Christophe Houde et à Gabriel Girard, de l'Université de Sherbrooke, pour leur aide méthodologique. Je remercie également Micheline Gravel, Manon Robert et toute l'équipe de la résonance magnétique du CHUM hôpital Notre-Dame pour leur aide technique.

Un remerciement spécial à Alan Tucholka, un collègue, un mentor, un ami.

Finalement, j'aimerais remercier du fond du cœur ma mère Mona, mon beau-père Albert, mon frère Joe, ma belle-sœur Marie et ma copine Charlotte pour leur amour, leur soutien et leurs encouragements absolus, sans qui je n'aurais pu réussir. Merci à François Filiatrault pour sa sagesse, son écoute et ses conseils.

Introduction

Historique

L’insula, le claustrum et le gyrus cingulaire sont des régions cérébrales voisines dont la connectivité et les fonctions étaient peu connues jusqu’à récemment. Selon Shelley et Trimble (2004) l’existence de l'insula est rapportée pour la première fois par André Vésale dans une gravure du septième livre de son *De Humani Corporis Fabrica* publié en 1543. C'est en 1641 qu'une première illustration spécifique de l'insula apparaît dans les *Institutiones Anatomicae* de Caspar Bartholin. En 1783, Alexander Monro a représenté les trois gyri antérieurs sans toutefois les nommer ou les décrire. Leur première description naît en 1786 quand Félix Vicq-d'Azyr la définit comme une convolution située entre le sillon latéral et le striatum. En 1809, le médecin allemand Johann Christian Reil mentionne la région dans l'ouvrage anatomique le plus influent de son temps et lui donne son nom : l'île de Reil (Binder, Schaller, & Clusmann, 2007). Quatre-vingts ans plus tard, la description anatomique, et morphologique, incluant la terminologie de l’insula est dressée par Oskar Eberstaller (Eberstaller, 1887); considérée comme la plus complète, elle servit longtemps de référence. Dès lors, plusieurs articles concernant l’insula, considérés fondateurs, ont été publiés, lesquels rapportaient des découvertes novatrices telles que la cartographie cytoarchitectonique des aires de Brodmann (BA; Brodmann, 1909; O. Vogt & Vogt, 1903), les neurones Von Economo, l’illustration des modèles sulco-gyraux de l’insula (C von Economo, 1929), puis la myéloarchitecture et la cytoarchitecture décrite par Clarke & O’Malley (1968).

Finalement, Penfield, dans les années 1950, évoque une connexion fonctionnelle probable entre les régions insulaires et temporales par enregistrement électroencéphalographique chez des patients épileptiques (Penfield & Faulk, 1955; Penfield & Jasper, 1954) tandis que Mesulam et Mufson, dans les années 1980, décrivent les connexions afférentes et efférentes chez les primates non humains et cartographient les réseaux viscéral et somesthésique de l'insula (Mesulam & Mufson, 1982a, 1982b; Mufson & Mesulam, 1982), faisant œuvre de pionniers dans le domaine.

Anatomie

L'insula est une structure située profondément dans le sillon latéral de façon bilatérale et possède une forme pyramidale inversée représentant environ 1 % à 4 % de la surface corticale (Semendeferi et al. 2000). Sa pointe, l'apex, se situe au niveau antéro-inférieur et représente la partie la plus superficielle de l'insula. Celle-ci est divisée par le sillon central insulaire en une partie antérieure composée de trois courts gyri (antérieur, moyen et postérieur) et en une partie postérieure composée de deux longs gyri (antérieur et postérieur) (Augustine, 1996; Flynn, 1999; Türe, Yaşargil, Al-Mefty, & Yaşargil, 1999). Ces gyri insulaires forment un motif en éventail et convergent au niveau antérieur et inférieur vers l'entrée vasculaire de cette région, le limen insulae, qui contient le faisceau uniforme rassemblant les fibres de matières blanches sous-jacentes. Les gyri courts moyen et postérieur se situent au niveau de la jonction orbitofrontale (Türe et al., 1999) et les régions suivantes se situent directement sous le cortex insulaire : la capsule extrême, le claustrum, la capsule externe (abritant le faisceau arqué), le noyau lenticulaire et la capsule interne.

L'insula est considérée comme le cinquième lobe du cerveau et constitue la quatrième région cartographique de Brodmann, qui lui attribue les aires 13 à 16 (Brodmann, 1909) (Stephani, Fernandez-Baca Vaca, Maciunas, Koubeissi, & Lüders, 2011). Les études histologiques ont rapporté une division architectonique de l'insula qui ne suit pas nécessairement sa division sulco-gyrale. Elle est plutôt divisée en trois zones selon son organisation, sa forme, le nombre et les types de neurones, le tout arrangé de façon centrifuge : a) la zone agranulaire, phylogénétiquement plus ancienne et moins différenciée (allocortex agranulaire), située de manière rostro-ventrale au limen insulae; b) la zone granulaire, mieux différenciée (isocortex ou néocortex granulaire) et positionnée caudo-dorsalement, couvrant l'insula postéro-dorsale; c) la zone de transition (ou intermédiaire) disgranulaire, allant de la région antérieure à la région postérieure de l'insula (Mesulam & Mufson, 1985). Les termes granulaire et agranulaire réfèrent à la présence ou l'absence d'une couche granulaire interne (IV). Dans la zone agranulaire, deux zones architectoniquement distinctes sont identifiées, une qui possède une *lamina dissecans* et l'autre non (Augustine, 1996; Preuss & Goldman-Rakic, 1989). La zone intermédiaire est dite disgranulaire parce que les cellules granuleuses sont rares dans la zone IV et n'affichent pas la différentiation laminaire complète. Une caractéristique particulière de l'insula antérieure est que nous retrouvons au niveau de la cinquième couche, en plus des neurones pyramidaux, de larges cellules fusiformes aussi appelées neurones von Economo, qu'on observe également dans le gyrus cingulaire antérieur (Cauda et al., 2013; Constantin von Economo, 1926; Nieuwenhuys, 2012). L'aire rétroinsulaire, postérieure à l'insula, à la jonction entre les opercules pariétal et temporal, possède une cytoarchitecture intermédiaire entre la zone granulaire et le cortex temporopariétal (Augustine, 1996; E. G. Jones & Burton, 1976).

Fonctions majeures de l'insula

Le rôle de l'insula est longtemps demeuré énigmatique, en raison de sa localisation en profondeur et de la très faible incidence des lésions circonscrites à cette région (Cereda et al., 2002). Les travaux de stimulation électro-corticale entrepris par Penfield au milieu du 20e siècle (Penfield and Faulk, 1955), et surtout l'avènement des techniques de neuro-imagerie fonctionnelle, ont permis une meilleure compréhension du rôle complexe joué par cette structure dans le fonctionnement neuropsychologique. Étant donné sa connectivité disparate à travers le cortex, il n'est pas étonnant que l'insula soit impliquée dans une multitude de fonctions. En effet, une méta-analyse de Kurth et al. (2010), portant sur 811 études concernant l'activation de l'insula lors de diverses tâches, a établi quatre principaux groupes de fonctions, lesquels impliqueraient des sous-régions insulaires distinctes : les fonctions sensorimotrices au sein des portions moyenne et postérieure de l'insula, les fonctions olfacto-gustatives le long du sillon central de l'insula droit, les fonctions socioémotionnelles dans l'insula antéro-ventrale, et les fonctions cognitives, qui convergeraient dans la partie antéro-dorsale de l'insula. La connectivité anatomique (Behrens et al., 2003) ou fonctionnelle (B. B. Biswal et al., 2010; Honey et al., 2009) entre l'insula et d'autres régions sous-entend que celles-ci jouent un rôle dans des fonctions similaires.

Fonctions sensorielles et motrices

Les premières études de stimulation électro-corticale de l'insula chez l'humain auprès de patients épileptiques ont rapporté un ensemble de sensations et de mouvements viscéraux et somatiques, incluant des sensations de nausées, des sensations de mouvements gastriques et abdominaux, de même que des sensations de picotement au visage et dans les membres supérieurs (Penfield & Faulk, 1955). Le rôle de l'insula dans la perception des sensations viscérales a d'ailleurs mené des auteurs à proposer que cette structure constitue le siège de l'interoception, soit la fonction permettant de détecter les sensations internes ainsi que les changements à l'intérieur du corps (Craig, 2003). Celle-ci serait impliquée dans le syndrome du membre fantôme chez les personnes ayant un membre amputé et chez ceux souffrant d'anosognosie (Heydrich & Blanke, 2013; H.-O. Karnath, Baier, & Nägele, 2005). L'insula interviendrait également dans la conscience propre des membres et actions d'une personne (H.-O. Karnath & Baier, 2010). Un autre aspect bien établi de l'insula dans les perceptions sensorielles est son rôle dans le traitement de la douleur. En effet, tant les études de neuro-imagerie que les études de lésion et de stimulation électro-corticale tendent à supporter une contribution unique de la portion postérieure de l'insula et de l'opercule pariétal dans l'expérience de la douleur (Mazzola et al., 2009; Starr et al., 2009; Brooks et al. 2007; Afif et al. 2008).

Des travaux plus récents ont permis de répliquer les réponses viscérales et somatiques, en plus de rapporter des réponses dans d'autres modalités sensorielles, principalement les modalités auditive, gustative et olfactive (Nguyen et al. 2009; Stephani et al., 2011). L'insula semble jouer un rôle multiple dans le traitement central des informations auditives, comme en

font foi les multiples déficits auditifs pouvant résulter d'une lésion insulaire (Bamiou et al., 2003, 2006). Une étude récente met également en lien l'insula et l'hyperacousie (Boucher et al., 2015). Cette étude, de même que les observations d'altération de l'intensité du goût et des odeurs à la suite d'une lésion insulaire isolée (Mak et al., 2005), sont compatibles avec un rôle de l'insula dans le traitement de la douleur et de la magnitude des stimuli à un niveau multisensoriel.

Quant au goût, l'insula antérieure est activée suite à une stimulation orale somatosensorielle (toucher) par le goût oral, la texture et les sensations viscérales (Rolls, 2015), mais aussi par l'aspect hédonique du système de récompense face à la nourriture (Frank et al. 2013). Elle jouerait un rôle dans la détection de la qualité, l'intensité, la concentration et l'agréabilité du goût, et de ce fait, est considérée comme le cortex gustatif (Dalenberg, Hoogeveen, Renken, Langers, & ter Horst, 2015; Small, 2010; Yaxley, Rolls, & Sienkiewicz, 1990). De plus, selon les études faites chez les macaques, il semblerait que l'insula antérieure soit impliquée dans les propriétés non gustatives telles que la texture et la température de la nourriture, rendant cette région impliquée dans l'analyse et l'intégration d'informations reliées à la nourriture (Verhagen, Kadohisa, & Rolls, 2004).

Fonctions socioémotionnelles

Les tâches émotionnelles dans les études fonctionnelles activent plusieurs régions du cerveau dont les cortex préfrontal médian, cingulaire antérieur, insulaire ainsi que l'amygdale (Phan, Wager, Taylor, & Liberzon, 2002). En effet, les émotions personnelles telles que la joie, la tristesse, la peur et le dégout, ainsi que les émotions sociales comme l'empathie, la

compassion ou celles touchant aux relations interpersonnelles comme la justice et la coopération, activent toutes l'insula (Lamm & Singer, 2010). De plus, celle-ci jouerait un rôle de mise en contexte des émotions, qu'elles soient négatives ou positives (Damasio et al. 2000). Les patients ayant une lésion insulaire seraient capables de percevoir la nature émotionnelle d'un stimulus, mais incapables d'avoir une réponse affective appropriée (Jones et al. 2010). Ceci suggère que l'insula pourrait être impliquée dans la modulation ou dans l'expérience subjective des émotions.

Des études en IRMf et en PET rapportent qu'un sentiment d'empathie activerait le réseau comprenant le cortex cingulaire antérieur dorsal et moyen antérieur, l'aire motrice supplémentaire et l'insula antérieure bilatérale (Fan et al., 2011). Elle pourrait être en lien avec la douleur (Gu et al., 2010; Mazzola et al., 2010), les sentiments et l'incertitude (Singer, Critchley, & Preuschoff, 2009).

Fonctions cognitives

De par son rôle dans le traitement des informations émotionnelles, l'insula semble intervenir dans les fonctions exécutives « chaudes », soit les fonctions de haut niveau affectées par l'état affectif, comme la prise de décision, la prise de risques (Clark et al., 2008; Weller, Levin, Shiv, & Bechara, 2009) et la prise de conscience de ses erreurs (Klein, Ullsperger, & Danielmeier, 2013; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010). L'insula antérieure ferait également partie du réseau de contrôle cognitif impliquant plusieurs tâches de performance telles que la recherche visuelle, la mémoire de travail (antéro-dorsal), la mémoire épisodique et à court terme (antéro-dorsal droit) et l'aptitude au changement de tâche (Vincent

et al. 2008; Sridharan et al. 2008; Dosenbach et al. 2007). De plus, l'insula ferait partie d'un réseau appelé *salience network*, dont le cortex cingulaire fait aussi partie, touchant ainsi à la communication, au comportement social, à la conscience de soi, via l'intégration sensorielle, émotionnelle et l'information cognitive (Cauda et al., 2012; a D. B. Craig, 2009; V. Menon & Uddin, 2010; Seeley et al., 2007).

Le cortex insulaire antérieur joue un rôle dans la motricité impliquée dans le langage, notamment la programmation motrice, l'articulation, l'expression, la réceptivité, la production et la perception du langage (Afif, Minotti, Kahane, & Hoffmann, 2010; Bohland & Guenther, 2006; Dronkers, 1996). Étant donné qu'il est étroitement connecté à l'aire de Broca, il pourrait également avoir un rôle dans la coordination cognitive de haut niveau de la parole et de la production du langage (Ackermann & Riecker, 2010; Oh, Duerden, & Pang, 2014). L'insula est aussi impliquée dans la compréhension du langage des signes (Allen, Emmorey, Bruss, & Damasio, 2008). Les activations recensées peuvent être attribuées à l'insula en raison de sa position à mi-chemin entre les aires de Broca et de Wernicke, étant donné que celles-ci sont reliées par le fascicule arqué (Damasio, Damasio, & Chui, 1980). Cela remettrait ainsi en cause le rôle direct du cortex insulaire dans le langage (Ackermann & Riecker, 2010; C. L. Jones, Ward, & Critchley, 2010).

Psychopathologies

Conformément à son intégration multimodale, l'insula semble également impliquée dans certaines psychopathologies. Parmi elles, on retrouve l'obésité et les troubles alimentaires (Frank et al. 2015), le trouble d'anxiété généralisé (Baur et al. 2010), le trouble

dépressif (Paulus et al. 2010; Takahashi et al. 2010) les dépendances aux drogues telles que la nicotine (Sutherland et al. 2013; Naqvi et al. 2007) ou la cocaïne (Cisler et al. 2013; Wisner et al. 2013), le trouble du spectre de l'autisme (Uddin et al. 2009), la démence fronto-temporale (Seeley et al. 2010), la maladie de Parkinson (Christopher et al. 2014) ainsi que la schizophrénie (Wylie et al. 2010).

Connectivité insulaire chez les primates non humains

Suite à la découverte, au milieu du 20^{e} siècle, des méthodes de traçage telles que les acides aminés tritiés et la peroxydase de raifort (qui permettent le traçage axonal des chemins neuronaux par l'utilisation de transporteurs antérograde et rétrograde) (Oztas, 2003), l'étude du cortex insulaire est devenue proéminente chez les primates non humains. Le transport axonal rétrograde permet d'identifier les cellules d'origine des fibres nerveuses afférentes à une zone cible particulière tandis que le transport axonal antérograde permet à la cible de projection de groupes de cellules individuelles d'être cartographiée dans le système nerveux central (Köbbert et al., 2000).

Les études sur l'insula chez les macaques nous intéressent particulièrement parce que l'architecture de l'insula chez le singe est celle qui se rapproche le plus de celle de l'humain. Le travail cumulatif des 30 dernières années a démontré que le cortex insulaire est connecté au cortex cérébral (lobes frontal, temporal et pariétal), aux ganglions de la base, à certaines régions limbiques et paralimbiques comme l'amygdale, ainsi qu'au thalamus.

Lobe frontal

Le cortex insulaire envoie des projections efférentes diffuses vers le lobe frontal : l'aire 6 (homologue à l'aire 6 frontale agranulaire chez l'humain, composée du cortex prémoteur et de l'aire motrice supplémentaire) incluant l'aire F3 (aire motrice supplémentaire) et F6 (aire motrice présupplémentaire), le cortex préfrontal (incluant le gyrus frontal inférieur, l'opercule frontal et le cortex orbitofrontal) ainsi que le gyrus cingulaire (Aires 23, 24) (Mufson & Mesulam, 1982). Dans leurs travaux, Mesulam et Mufson ont trié les connexions par secteurs architectoniques. La zone agranulaire de l'insula envoie des projections vers les aires cingulaires antérieures 24a et 24b, alors que la zone granulaire envoie des projections vers l'aire cingulaire postérieure 23 (Mesulam & Mufson, 1982a; B. a Vogt, Pandya, & Rosene, 1987; B. a Vogt & Pandya, 1987). La zone insulaire disgranulaire envoie des projections vers l'aire frontale F6 (aire motrice présupplémentaire), l'opercule frontal, le cortex frontal ventral granulaire et le cortex orbitofrontal. La zone granulaire de l'insula possède des connexions efférentes vers le cortex frontal ventral granulaire ainsi que vers l'aire frontale F3 (aire motrice supplémentaire). Les connexions afférentes frontales vers l'insula ont pour origine le cortex préfrontal, le cortex orbitofrontal (incluant le bulbe olfactif) et l'opercule frontal.

Lobe pariétal

Le cortex insulaire partage des connexions réciproques avec les cortex somatosensoriels primaire et secondaire, incluant l'opercule pariétal, l'aire 5 et l'aire rétroinsulaire (Augustine, 1996; Mesulam & Mufson, 1982a). Architectoniquement, on suppose que le cortex somatosensoriel secondaire se connecte de façon réciproque aux zones

disgranulaire et agranulaire de l'insula, alors que l'aire rétroinsulaire se connecte de façon réciproque à la zone granulaire de l'insula.

Lobe temporal

Le cortex insulaire envoie des projections efférentes vers le pôle temporal, le sillon temporal supérieur et le planum temporal. Les connexions afférentes du lobe temporal atteignant le cortex insulaire proviennent du cortex auditif (cortex auditif primaire, cortex auditif associatif, cortex post-auditif), de l'opercule temporal, du cortex temporal supérieur/sillon temporal supérieur et du pôle temporal. Au niveau architectonique, la zone agranulaire de l'insula projette vers la zone disgranulaire du pôle temporal, le sillon temporal antérieur supérieur et le cortex auditif primaire (Augustine, 1996; Mufson & Mesulam, 1982). La zone disgranulaire de l'insula antérieure projette vers la zone disgranulaire du pôle temporal, du sillon temporal antérieur supérieur, de la portion prépiriforme du cortex olfactif et des cortex prorhinal et entorhinal. La zone disgranulaire de l'insula postérieure se connecte au sillon temporal antérieur supérieur (Augustine, 1996; Mufson & Mesulam, 1982). Enfin, il est probable que la zone granulaire de l'insula envoie aussi des projections vers le cortex temporo-polaire. La zone disgranulaire de l'insula reçoit des projections afférentes du sillon temporal supérieur et du cortex temporo-polaire. La zone granulaire de l'insula reçoit aussi des connexions afférentes du cortex temporo-polaire.

En temporal médian, le cortex insulaire possède des connexions réciproques avec l'amygdale. La zone disgranulaire envoie des projections vers les noyaux latéraux de l'amygdale et vers les aires amygdaloïdes corticale et médiale. La zone granulaire de l'insula envoie des projections vers les noyaux basaux latéraux de l'amygdale et reçoit des projections du noyau latéral de la

partie basolatérale de l'amygdale. D'autres structures mésio-temporales possèdent des connexions avec le cortex insulaire, incluant le cortex périamygdaloïde, l'hippocampe antérieur, les cortex entorhinal/prorhinal/périrhinal, le cortex piriforme temporal et le noyau endo-piriforme, et le gyrus parahippocampique. Architectoniquement, il existe des connexions connues provenant de la zone granulaire de l'insula vers les cortex périamygdaloïde, prorhinal, entorhinal, et de la zone disgranulaire de l'insula vers le cortex périrhinal. Il existe aussi des projections du cortex entorhinal vers la zone agranulaire de l'insula, mais moins fréquentes vers les zones disgranulaire et granulaire de l'insula.

Structures sous-corticales

Les études animales ont révélé que le cortex insulaire est connecté de façon réciproque avec plusieurs noyaux thalamiques (spécialement le thalamus dorsal), les noyaux gris centraux (notamment, le noyau lentiforme, la queue du caudé, le putamen et le claustrum) et l'hypothalamus. Il existe aussi des connexions du cortex insulaire entrant dans la matière blanche vers la capsule interne, la capsule externe, la commissure antérieure et le corps calleux (Augustine, 1996; Berke, 1960).

Connectivité structurelle chez l'humain

Ce n'est qu'au courant de la dernière décennie, grâce aux avancements méthodologiques de l'imagerie par résonance magnétique, que les études sur la connectivité structurelle chez l'humain se sont développées.

Seules trois études ont examiné la connectivité structurelle de l'insula chez l'humain (Cerliani et al., 2012; Cloutman, Binney, Drakesmith, Parker, & Lambon Ralph, 2012; Jakab, Molnár, Bogner, Béres, & Berényi, 2012), et une sur son développement pendant l'adolescence (Dennis et al., 2014). La première étude, par Cloutman et al. (2012), a examiné 20 sujets en utilisant une imagerie par résonance magnétique (IRM) à 3 Tesla et la méthode par index de connectivité probabiliste (Parker, Haroon, & Wheeler-Kingshott, 2003) afin d'échantillonner la probabilité de l'orientation des fonctions de densité (J.-D. D. Tournier et al., 2008), générée en utilisant la méthode de déconvolution sphérique contrainte permettant d'augmenter la résolution angulaire (Descoteaux, Deriche, Knösche, & Anwander, 2009). L'objectif était de cartographier la connectivité structurelle des sous-régions insulaires. Vingt-mille fibres ont été estimées à partir de chaque voxel avec une « taille de pas » de 0,50 mm et une valeur d'arrêt des courbures d'angle d'un maximum de 180º ou une longueur maximale de 500 mm. La boîte à outils DARTEL (Ashburner, 2007) sous SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/ spm8) a été employée pour la normalisation. Le chemin des fibres a été déterminé en utilisant les masques des régions du cerveau obtenus avec l'atlas « Automated Anatomical Labeling » (AAL) (WFU Pick Atlas -Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). Sept régions d'intérêt ont été créées afin d'explorer les différences topographiques ou cytoarchitecturales de la connectivité insulaire entre les régions antérieure et postérieure ainsi que dorsale et ventrale. En ayant recours à la tractographie probabiliste, les auteurs ont rapporté des connexions similaires dans les deux hémisphères. Le modèle de connectivité dévoile trois sous-divisions insulaires, une région antérieure, une postérieure et une intermédiaire. Les résultats montrent que la région antérieure semble connectée avec les régions orbitofrontale et inférieure frontale (triangularis

et opercularis), la région temporale antérieure, le gyrus temporal moyen postérieur suivant un chemin exclusif impliquant les fibres du faisceau unciné, la capsule extrême et le faisceau fronto-occipital. La région postérieure est principalement connectée avec les aires temporales postérieure supérieure, antérieure supérieure et moyenne, l'opercule frontal à travers les chemins dorsal et ventral impliquant la capsule extrême et le faisceau arqué. La région intermédiaire est rapportée comme ayant un schéma de connectivité graduée et hybride aux régions frontale et temporale, l'opercule rolandique, les gyri postcentral et supramarginal, via une voie essentiellement dorsale. Ces découvertes sont en accord avec les études humaines en IRMfer (Cauda et al., 2011; Deen, Pitskel, & Pelphrey, 2011) et les études susmentionnées chez les primates non humains.

La deuxième étude, publiée par Cerliani et al. (2012), a examiné dix sujets au moyen d'une IRM à 3 Tesla et a utilisé la boîte à outils de diffusion FMRIB afin d'effectuer une tractographie probabiliste. Pour chaque voxel, une population de fibres a été générée à partir de 5000 faisceaux, permettant d'obtenir une matrice de connectivité comprenant les voxels atteints et le nombre de fibres croisant chacun des voxels. Les régions d'intérêt ont été créées en utilisant la méthode de Naidich et al. (2004) afin d'identifier les repères anatomiques et de déterminer la terminologie (Türe et al., 1999). Seuls les voxels ayant plus de 50 échantillons et présents dans au moins la moitié des cerveaux examinés ont été analysés. Les auteurs ont trouvé un patron de connectivité rostrocaudal. L'insula antérieure projette vers le cortex orbitofrontal, le gyrus inférieur frontal, la partie dorsale du lobe temporal, le noyau centromédian et le complexe latérobasal de l'amygdale. L'insula dorso-caudale projette vers le lobe pariétal, les régions postérieures du lobe temporal, le gyrus frontal inférieur, le cortex préfrontal dorsolatéral gauche et les régions extrastriées du cortex occipital. Les régions

insulaires moyennes possèdent un patron de connectivité mixte entre l'insula antérieure et postérieure et sont surtout connectées au cortex prémoteur, aux lobes temporal et pariétal, au gyrus frontal inférieur ainsi qu'au cortex orbitofrontal. De plus, une connectivité asymétrique a été rapportée dans l'hémisphère droit avec l'AB 44 (gyrus frontal inférieur) et le lobule pariétal supérieur, alors que dans l'hémisphère gauche, ce sont plutôt les régions limbiques et l'AB 6 (cortex prémoteur et l'aire motrice supplémentaire). Ces résultats corroborent avec les découvertes de Cloutman et al. (2012).

La troisième étude, publiée par Jakab et al. (2012), a examiné 40 sujets ayant passé une IRM à 1.5 Tesla. Le but était d'observer l'organisation du cortex insulaire chez l'humain en se basant sur les similarités de ses projections distantes. La tractographie probabiliste a été lancée en utilisant la boîte à outils de diffusion FMRIB. Les images de diffusion ont été normalisées sur le modèle d'anisotropie fonctionnelle de FSL dans l'espace standard de l'Institut Neurologique de Montréal (MNI152) en utilisant un enregistrement non linéaire. L'atlas d'Harvard-Oxford dans l'espace du MNI152 a été utilisé afin d'extraire les régions insulaires et, pour chaque sujet, les régions d'intérêt ont été définies sur l'espace natif de la T1. Un algorithme de regroupement par *k-mean* sur la matrice de connectivité a divisé l'insula en deux régions distinctes : une antérieure et une postérieure, pour chaque hémisphère. La première montre des projections avec le thalamus dorso-médian, les lobes temporal et occipital, les gyri orbitofrontal et frontal inférieur. Pour la seconde région, des connexions avec les lobes frontal et pariétal ainsi que le thalamus ventro-latéral ont été observées. Tout comme les résultats de Cerliani et al., (2012), aucune connexion avec le lobe occipital n'a été rapportée.

Méthodologie

Les récentes avancées en neuro-imagerie fonctionnelle et structurelle ont permis de mieux déceler le profil de connectivité de l'insula chez l'humain. Les méthodes d'investigation par IRM se distinguent selon l'approche fonctionnelle et l'approche structurelle, chacune ayant ses avantages et ses limites. La connectivité structurelle permet d'estimer le nombre de fibres reliant les différentes régions du cerveau. La connectivité fonctionnelle permet d'inférer les connexions entre les régions d'intérêt d'un réseau en identifiant les patrons communs entre les fluctuations du signal, spatialement séparées, des composantes du système.

IRMf

L'imagerie par résonance magnétique fonctionnelle (IRMf) est une technique de neuro-imagerie non invasive qui est sensible aux variations de concentration en désoxyhémoglobine, et qui permet de cartographier les régions anatomo-fonctionnelles du cerveau en fonction de leurs activations spécifiques au cours des tâches (Logothetis, 2008). Cette technique est surtout utilisée pour corréler les activations fonctionnelles de régions cérébrales avec les connaissances a priori basées sur une analyse de corrélation croisée. De nombreuses études d'IRMf ont rapporté des activations de l'insula, que cette région ait été le centre d'intérêt ou qu'il s'agisse de découvertes collatérales, ce qui est fort probablement attribuable à son rôle intégratif et multimodal (voir le numéro spécial de *Brain Structure and Function* sur l'insula, 2010). Les paradigmes se rapportant aux émotions et à l'empathie, à différentes modalités sensorielles (olfaction, gustation, somatosensation et interoception), à la douleur, à l'attention,

au langage, et à la mémoire sont fréquemment rapportés comme activant le cortex insulaire (Cauda et al., 2012; Kurth et al., 2010; Mutschler et al., 2009; Wager & Barrett, 2004; Chang et al. 2012). Dans la plus récente méta-analyse (Kurth et al., 2010), les auteurs ont fait une revue scientifique sur l'estimation de la probabilité d'activation de 1 768 expériences fonctionnelles en neuro-imagerie comportant une activation insulaire (811 articles; 11 796 sujets). Cela donne une idée de la variété des rôles que peut jouer l'insula. Le domaine de l'imagerie fonctionnelle étant trop large et ne faisant pas partie directement de l'objet de ce mémoire, les résultats des études cités précédemment ne seront pas revus en détail.

Limites

L'IRMf mesure essentiellement un signal de remplacement soumis à des restrictions spatiotemporelles basées sur deux contraintes principales (Logothetis, 2008) : 1) la contrainte physique, par exemple une faible résolution spatiale par rapport aux images anatomiques (3 à 5 mm pour une IRMf, tandis que l'épaisseur corticale varie entre 1 à 4 mm (B Fischl, Fischl, Dale, & Dale, 2000) conduisant à un effet de volume partiel), les temps de relaxation et le bruit thermique; 2) les facteurs physiologiques, tels que le rythme cardiaque et la respiration ou les mouvements des sujets (pour une revue scientifique, voir Constable, 2012). Ensuite, la faible résolution temporelle (généralement autour de 1 volume toutes les 3 secondes pour les protocoles récents d'IRMf) rend difficile de différencier les modèles d'activation résultant de stimuli immédiats. Différentes approches telles que les designs par blocs, l'analyse indépendante, le marquage de *spin* artériel ou liées à l'événement (*event related*) existent et diffèrent dans leurs méthodes et leurs résultats. Ceux-ci reposent essentiellement sur la linéarité entre l'activité neuronale et les réponses hémodynamiques, alors que les processus

cérébraux sont fortement non linéaires (Detre & Wang, 2002; Li, Guo, Nie, Li, & Liu, 2009; Logothetis, 2008). De même, les cartes obtenues par IRMf sont une moyenne des représentations statiques de l'activité dynamique du cerveau sur une longue période de temps par rapport au temps requis pour le traitement de l'information mentale (R. S. Menon & Kim, 1999). Les plans d'étude ne prennent pas en considération les circuits et l'organisation fonctionnelle du cerveau, tandis que les paramètres, tels que le seuil statistique, sont choisis arbitrairement (Constable, 2012; Logothetis, 2008). Par conséquent, les expériences d'IRMf liées aux tâches doivent être interprétées avec prudence. Enfin, les tâches doivent être conçues avec soin et l'analyse peut être particulièrement laborieuse lorsque l'on considère les processus qui sont conceptuellement difficiles ou qui ne possèdent pas une tâche facile à définir. Il y aura toujours une certaine équivoque dans la catégorisation des processus cognitifs. Par exemple, la douleur et l'interoception ne sont pas seulement des processus sensoriels, mais peuvent également avoir une composante émotionnelle et empathique importante. Cette ambiguïté s'applique également, à un certain niveau, à presque toutes les catégories de tâches (Kurth et al., 2010).

IRMf à l'état de repos

L'IRMfer est une technique qui permet d'étudier les systèmes fonctionnels de l'activation neuronale du cerveau à l'état de repos. Plus précisément, elle illustre l'activation synchronisée entre les différentes régions du cerveau spatialement distinctes et en l'absence de tâches (Lee, Smyser, & Shimony, 2013; Thomason et al., 2011; Wurina, Zang, & Zhao, 2012). La majorité des études en IRMfer sur la connectivité fonctionnelle du cortex insulaire sont

décrites selon une division antéro-postérieure. L'insula antérieure a surtout été activée en même temps que les cortex frontal, pariétal et temporal, le gyrus cingulaire, les ganglions de la base, le thalamus et l'amygdale. L'insula postérieure aurait des activations avec les opercules frontal, pariétal et temporal, le cortex cingulaire antérieur dorsal, le cortex cingulaire postérieur, le thalamus, les gyri précentral et postcentral ainsi que le lobe occipital. Certaines régions ont été rapportées comme ayant une activation simultanée avec l'insula, mais uniquement dans certaines études. Parmi elles, on retrouve le cervelet, la protubérance et les ganglions de la base qui s'activaient simultanément avec le cortex insulaire droit alors que le putamen s'activait avec le cortex insulaire (Cauda et al., 2011).

Limites

Les deux principales limites de l'IRMfer sont la présence de bruits physiologiques tels que le rythme cardiaque et la respiration, et la fluctuation du signal (Birn, 2012). Une deuxième limitation majeure est l'absence de traitement de données standard avec des images IRMfer. Il existe plusieurs méthodes disponibles, telles que la connectivité fonctionnelle à base de *seeds* (B. Biswal, Yetkin, Haughton, & Hyde, 1995), l'analyse par composantes indépendantes (Kiviniemi, Kantola, Jauhiainen, Hyvärinen, & Tervonen, 2003), le regroupement, la classification par motifs (Norman, Polyn, Detre, & Haxby, 2006), la théorie des graphes et des méthodes locales, chacune présentant des avantages et des inconvénients (pour une revue scientifique, voir Margulies et al., 2010). En fonction du choix de la technique, la présence de faux positifs ou de faux négatifs est plus ou moins importante. En outre, certaines méthodes nécessitent une connaissance a priori, basée sur des données déjà

existantes, ou une méthode basée sur un modèle, ce qui est utile pour les études où aucune information n'est connue sur la résolution spatiale et temporelle de l'IRMfer (Li et al., 2009).

Tractographie

L'imagerie de diffusion est une technique d'IRM in vivo qui utilise les gradients de champ magnétique, envoyés dans plusieurs directions suivant une sphère, permettant d'obtenir de l'information sur la diffusivité des molécules d'eau des tissus du cerveau. Les faisceaux de fibres forcent celles-ci à suivre leur direction; si les gradients et les molécules d'eau possèdent la même direction, il y aura alors une baisse de signal. L'imagerie par tenseur de diffusion (ITD) utilise cette information afin de fournir l'orientation des molécules d'eau dans chacun des voxels ainsi que son anisotropie de diffusion, permettant l'estimation de l'organisation axonale du cerveau. L'ITD estime uniquement la direction principale et ne peut différencier entre un manque de diffusivité et une diffusivité égale dans toutes les directions, évitant ainsi l'analyse des fibres qui se croisent, qui constituent la majeure partie du cerveau. L'imagerie à haute résolution de diffusion angulaire (IHRDA) requiert plus de directions (un strict minimum de 15, mais une moyenne de 40 directions est requise afin de déduire correctement les multiples directions) comparativement au minimum de six requises en ITD. Cette dernière estime la probabilité que deux régions soient connectées sur une population d'une fibre par voxel, alors que l'IHRDA traque les fibres de matière blanche sur une population de fibres multiples par voxel, réduisant ainsi les faux négatifs. Le traçage de fibres peut être induit grâce à ces méthodes et représente la seule technique non invasive qui permet d'étudier in vivo les fibres de matière blanche du cerveau chez l'humain (Jbabdi & Johansen-Berg, 2011; Le

Bihan, 2003; Mori & Van Zijl, 2002; Mori & Zhang, 2006; J. D. Tournier, Calamante, & Connelly, 2012; Tuch et al., 2002). Le principe derrière le traçage de fibres consiste à créer des régions d'intérêt en utilisant comme point de repère des *seeds* où une estimation de la population des fibres suivra la direction principale pas à pas. Le chemin tracé s'appuie sur l'orientation des fibres les plus proches de celles choisies précédemment. Afin d'éviter les faux positifs, certaines contraintes sont requises, comme l'implémentation d'une limite de l'angle des courbures, de la distance totale (afin d'éviter les boucles) et des masques binaires ou probabilistes de matière blanche. Il n'existe malheureusement pas de critères standards, ce qui fait en sorte que différents résultats peuvent être rapportés dépendamment de la valeur des paramètres utilisés. De plus, il existe plusieurs logiciels d'analyses, méthodes et pipelines afin d'analyser la connectivité structurelle, ce qui rend difficile la comparaison entre les différentes études publiées.

Limites

Bien que la tractographie soit la méthode la plus avancée in vivo disponible pour étudier les faisceaux de matière blanche chez les humains et la plus proche des voies de traçage des animaux, elle n'est pas sans lacunes. Toutes les techniques de diffusion par tractographie ont une faible résolution spatiale, une absence de validation histologique et un manque de critères standards soutenus empiriquement pour déterminer la valeur des seuils et le nombre de projections (*streamlines*), et sont incapables de distinguer entre les projections afférentes et efférentes (Cerliani et al., 2012; Dell'Acqua & Catani, 2012). La tractographie probabiliste basée sur l'ITD estime la probabilité qu'il existe une voie entre les deux régions et elle est limitée à une direction de fibres par voxel, tandis que plusieurs directions de fibres

existent, ce qui rend le problème des croisements de fibres la principale limite de cette technique (Farquharson et al., 2013; Frank, 2002; Jakab et al., 2012; Jbabdi, Sotiropoulos, Savio, Graña, & Behrens, 2012; J. D. Tournier, Calamante, & Connelly, 2007; J.-D. Tournier, Mori, & Leemans, 2011). Par conséquent, la connexion ne peut être établie avec certitude et elle reste vulnérable à des erreurs de type I dans la région proche des *seeds* ainsi qu'à des erreurs de type II dans les régions plus éloignées (Cloutman et al., 2012; Jakab et al., 2012; D. K. Jones, 2008; Morris, Embleton, & Parker, 2008). Les petits faisceaux de fibres risquent d'être perdus lors de la traversée de plus grandes étendues comme le faisceau longitudinal et la *corona radiata* (Dougherty, Ben-Shachar, Bammer, Brewer, & Wandell, 2005). Les longs faisceaux sont plus difficiles à identifier puisque plus la voie est longue, plus il existe une probabilité que la connectivité diminue et que les projections (*streamlines*) se dispersent (Cloutman et al., 2012; Morris et al., 2008). Cela peut expliquer pourquoi aucune étude de tractographie n'a encore rapporté une connexion structurelle entre l'insula et le cortex cingulaire chez l'humain en dépit des résultats en IRMf, IRMfer, chez l'humain, et par traçage, chez les macaques, comme mentionné ci-dessus. De nouveaux algorithmes et approches sont en développement, comme l'imagerie du spectre de diffusion (DSI), qui peut aider à réduire les résultats faux négatifs et à détecter de façon plus optimale les croisements de fibres au sein de la matière blanche dans les structures corticales et sous-corticales (Wedeen et al., 2008). Les études humaines en tractographie qui ont été mentionnées ci-dessus se basent sur un nombre relativement faible de sujets et de régions d'intérêt établies sur une division sulco-gyrale. Malheureusement, les caractéristiques macroscopiques sulco-gyrales ne sont pas des repères fiables des frontières cytoarchitectoniques (Amunts et al., 1999; Bruce Fischl et al., 2008). En outre, la proximité d'autres faisceaux de matière blanche dans le cortex insulaire, comme la

capsule extrême (Makris & Pandya, 2009), la capsule externe, la *corona radiata*, le faisceau unciforme, le faisceau arqué (Nieuwenhuys, Voogd, & Van Hujzen, 1988) et le faisceau fronto-occipital inférieur, peuvent influer sur les résultats de tractographie en montrant, par exemple, des connexions avec le lobe occipital. Dans cette perspective, aucune étude chez l'homme ou l'animal n'a mis à jour des connexions structurelles entre le lobe occipital et le cortex insulaire; cependant, certains ont rapporté des connexions directes entre les régions pariéto-occipitales et le claustrum chez les animaux (Crick & Koch, 2005; Tanné-Gariépy, Rouiller, & Boussaoud, 2002), tandis que chez les humains, les connexions entre le claustrum et le lobe occipital ont été trouvées via le faisceau fronto-occipital inférieur (Catani & Thiebaut de Schotten, 2008; Cerliani et al., 2012; Schmahmann & Pandya, 2007; Schmahmann et al., 2007).

Position du problème

Il existe un vaste corpus d'études en IRMf rapportant une panoplie d'activations insulaires dans une grande variété de tâches (pour une revue scientifique, voir Cauda et al., 2011; Kurth et al., 2010). Certaines de ces études décrivent des co-activations entre l'insula et d'autres régions corticales connues pour avoir des connexions aussi chez les primates non humains. Puisque d'autres fonctions peuvent être testées lors des tâches en IRMf, des zones supplémentaires peuvent s'activer sans nécessairement avoir de liens avec l'insula. Pour cette raison, il est important de différencier ces activations dites aberrantes à l'aide d'approches novatrices telles que la tractographie. Les trois études en tractographie décrites précédemment ont suivi des méthodes de prétraitement standard et ont appliqué un algorithme probabiliste en

ITD (nombre de directions limitées) sur un faible échantillon. Étonnamment, aucune de ces études n'a rapporté de connexions avec le cortex cingulaire, bien que ce fut le cas dans les études chez les primates non humains (Mesulam & Mufson, 1982b; Mufson & Mesulam, 1982) et en IRMf (Cauda et al., 2011; Taylor, Seminowicz, & Davis, 2009). À la lumière de ces dernières, nous avons voulu éclaircir davantage la connectivité structurelle de l'insula en mettant l'emphase sur un plus grand nombre de participants et fondé sur l'état-des-connaissances des méthodes de prétraitement des données en imagerie de diffusion afin de mieux déceler les connexions corticales de l'insula. Pour ce faire, nous avons utilisé les dernières avancées en tractographie basée sur l'IHRDA, un algorithme déterministe, un nombre de sujets significatif et une parcellisation aléatoire, afin de surmonter, dans la mesure du possible, les limites connues telles que les croisements de fibres, la basse résolution des images ainsi que les connexions invalides telles que décrites dans Côté et al. (2013).

ARTICLE

The corticocortical structural connectivity of the human insula

Published by:

Cerebral Cortex, December 2015, in press

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Abstract

The insula is a complex structure involved in a wide range of functions. Tracing studies on nonhuman primates reveal a wide array of cortical connections in the frontal (orbitofrontal and prefrontal cortices, cingulate areas and supplementary motor area), parietal (primary and secondary somatosensory cortices) and temporal (temporal pole, auditory, prorhinal and entorhinal cortices) lobes. However, recent human tractography studies have not observed connections between the insula and the cingulate cortices, although these structures are thought to be functionally intimately connected. In this work, we try to unravel the structural connectivity between these regions and other known functionally connected structures, benefiting from a higher number of subjects and the latest state-of-the-art high angular resolution diffusion imaging (HARDI) tractography algorithms with anatomical priors. By performing an HARDI tractography analysis on 46 young normal adults, our study reveals a wide array of connections between the insula and the frontal, temporal, parietal and occipital lobes as well as limbic regions, with a rostro-caudal organization in line with tracing studies in macaques. Notably, we reveal for the first time in humans a clear structural connectivity between the insula and the cingulate, parahippocampal, supramarginal and angular gyri as well as the precuneus and occipital regions.

Keywords: insula, insular cortex, cingulate, tractography, diffusion.

Introduction

Located in the depth of the Sylvian fissure, the insula, a pyramidal-shaped structure, is considered as the fifth lobe of the brain (Stephani et al. 2011), and represents approximately 1-4% of the total cortical surface (Semendeferi and Damasio 2000). Topographically, the insula is covered laterally by the frontal, parietal and temporal opercula, while delimited medially by the extreme capsule, the claustrum, the external capsule (harboring the arcuate fasciculus), the lenticular nucleus and the internal capsule (Türe et al. 1999). It is divided by the central insular sillon into an anterior portion comprising 3 to 4 short gyri, and a posterior portion composed of 2 long gyri (anterior and posterior), which form a fan-like pattern (Flynn 1999). It is also divided into three architectonic zones based on its organization, shape, number and type of neurons: a) an agranular zone (Ia) located rostroventrally at the limen insulae; b) a granular zone (Ig) positioned caudodorsally covering the dorsal posterior insula and in between, c) a dysgranular transitional (or intermediate) zone (Id) spanning from the anterior to the posterior insula (Mesulam and Mufson 1985).

Cumulative work utilizing various techniques (electrophysiology, functional neuroimaging, positron emission tomography) along with lesion studies in primates, including humans, have established a role for the insula in a wide array of functions, including autonomic functions, viscero-sensory and motor function, motor association, vestibular function, language, somatosensation, chemosensation, central audition, emotions, pain, bodily awareness, self-recognition, attention, empathy, time perception, motivation, craving and addiction (for an extensive review, see Shelley and Trimble 2004; Kurth et al. 2010;

Nieuwenhuys 2012). These studies have also revealed different functional profiles between the left versus the right insula and the anterior versus the posterior insula.

Seminal work on non-human primates have demonstrated widespread connections between the insula and the frontal, temporal and parietal cortices, and limbic areas (Mesulam and Mufson 1982a, 1982b; Mufson and Mesulam 1982; Vogt and Pandya 1987), consistent with the wide variety of functions associated with this structure (see Augustine 1996). In humans, however, the structural connectivity of the insula is less documented. Comparative studies have shown that the insula has undergone a gradual increase in the complexity of its organization and size in the course of primate and hominid evolution (Semendeferi and Damasio 2000; Bauernfeind et al. 2013). The anatomical organization of insular sulci in humans is different from that of non-human primates, and it has been suggested that the greater size of some regions is correlated with newly emerged specialized functions such as empathy and social awareness (Semendeferi and Damasio 2000; Allen et al. 2002; Kaas 2013). Moreover, von Economo neurons (VENs; for a review, see Economo and Koskinas 1925; Economo 1926; Cauda et al. 2014) have been reported in humans, great apes, and more recently macaques (Evrard et al. 2012). The implication of these neurons in its connectivity map is still poorly known, but may play a role in a differential connectivity pattern (Cauda et al. 2014). Cross-species comparisons with humans have been challenging due to differences in investigative methods, such as tract-tracing that are not feasible on humans. However, recent developments in MRI-based diffusion-weighted imaging have made non-invasive study of structural connectivity possible in vivo with increasing precision and reliability.

To our knowledge, only three studies have investigated the structural connectivity of the human insula. Cloutman et al. (2012) recruited 24 subjects on a 3Testla MRI scan and used a dedicated software package using the PICo method to run a probabilistic tractography algorithm with 20000 streamlines per voxel, while using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002). Cerliani et al. (2012) scanned 10 subjects on a 3Tesla MRI scan using FMRIB's toolbox and a probabilistic tractography algorithm with 5000 seeds per voxel. Jakab et al. (2012) scanned 40 subjects on a 1.5Testla MRI scan using FMRIB's toolbox and probabilistic tractography algorithm with 1 seed per voxel. Their results showed that the anterior insular cortex has connections with the orbitofrontal cortex, the inferior and superior temporal gyri, the temporal pole, the thalamus and the amygdala; that the middle insular cortex has connections with the superior and inferior frontal gyri, the precentral, postcentral and supramarginal gyri, the inferior and superior temporal gyri, the orbitofrontal and the parietal cortices, while the posterior insular cortex has connections with the superior and inferior frontal gyri, the precentral and postcentral gyri, the inferior and superior temporal gyri, the parietal cortex and the putamen (reviewed in Ghaziri et al. 2014). Surprisingly, none of these studies reported connections with the cingulate gyrus, although these have been described in tracing studies in animals (Mesulam and Mufson 1982b; Mufson and Mesulam 1982) and functional studies in humans (Taylor et al. 2009; Cauda et al. 2011).

In light of these latter structural connectivity studies, that are based on DTI probabilistic tractography, standard templates and a low number of subjects in some cases, our objective was to further investigate the connectivity of the insular cortex in humans. We put an emphasis on regions known to be related with the insula in non-human primates' studies as well as human functional studies such as the cingulate, parahippocampal, supramarginal and

angular gyri among others, by using the latest state-of-the-art tractography methods. To do so, we based our study on state-of-the-art HARDI deterministic tractography with anatomical priors similar to (Smith et al. 2012), recruited a significant number of subjects, while using random parcellation, in order to overcome known methodological limitations such as crossing-fibers, low resolution and invalid connections as defined in Côté et al. (2013).

Materials and Methods

Participants

Forty-six healthy right-handed subjects between the age of 19 and 39 (mean age ± SD: 24.5 ± 4.8; 18 men and 28 women), with no history of neurological or psychiatric disorders, were recruited. Informed written consent was obtained from all participants for procedures approved by the Centre Hospitalier de l'Université de Montréal (CHUM) ethics board, in accordance with the latest revision of the declaration of Helsinki.

Data acquisition

MRI data was acquired on a 3T Achieva scanner (Philips, the Netherlands). The diffusion-weighted images were acquired with a single-shot spin-echo echo-planar pulse sequence (TR = 7.96 milliseconds; TE = 77 milliseconds; flip angle = 90^{o}; slices = 68; field of view = 230mm; matrix = 128 x 128; voxel resolution = 1.8 mm x 1.8 mm x 1.8 mm; readout bandwidth = 19.6 Hz/ pixels; echo-planar imaging direction bandwidth = 1572.5 Hz; 8-channel head coil; SENSE acceleration factor = 2). One pure T2-weighted image (b=0 second/mm^2) and 60 images with noncollinear diffusion gradients (b = 1500 second/mm^2)

were obtained. In addition, T1-weighted images were acquired using 3D T1 gradient echo (scan time = 8.11 minutes; TR = 8.1 milliseconds; TE = 3.8 milliseconds; flip angle = 8º; slices = 176; voxel size = 1 mm x 1 mm x 1 mm, FOV 230 mm x 230 mm).

Analyses

Anatomical images preprocessing

Anatomical T1-weighted images were preprocessed with the FMRIB's software library (FSL; v.5.0.1, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) (Smith et al. 2004; Woolrich et al. 2009; Jenkinson et al. 2012). The brain extraction tool (BET) (Smith 2002) was used to remove non-brain tissues, after which, images were segmented using FMRIB's automated segmentation tool (FAST) (Zhang et al. 2001) resulting into probabilistic maps of white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) for each subject.

Template creation

A template representing every subject in a unique referential space had to be created in order to generate a normalized parcellation of the cortex of each hemisphere. Advanced Normalization Tools (ANTS) (v. 1.5, http://stnava.github.io/ANTs/, last accessed November 27, 2015; Avants and Gee 2004; Klein et al. 2009; Avants et al. 2010) was used to create a template from our 46 anatomical T1-weighted images using a bi-directional diffeomorphic algorithm, generating matrices to pass from the template space to each native subject space and vice versa. The probabilistic GM maps of each subject were then resampled to the template space using a linear interpolation. An average map of GM in the normalized space

was then created, binarized, and manually cleaned to: 1) remove non-brain tissue (segmentation, artifacts), 2) remove the cerebellum, 3) separate left and right hemisphere, and 4) delineate the insular cortex in each hemisphere. Manual segmentation was performed using ITK-SNAP software (v.2.4.0, http://www.itksnap.org, last accessed November 27, 2015; Yushkevich et al. 2006) and was double checked by 2 different investigators.

Creation of the Regions of Interests

The binary cleaned cortex map of each hemisphere was randomly parcellated into 200 regions using a k-mean algorithm (Figs 1a and 2b). As for the insular cortex, each hemispherewas manually segmented by following a sulco-gyral division. Based on previous studies (Türe et al. 1999; Naidich et al. 2004; Tanriover et al. 2004; Afif et al. 2009; Afif and Mertens 2010; Cohen et al. 2010) and following the nomenclature of Türe et al. (1999), we first segmented the insula using a sagittal view, starting from the limit of the dorsal anterior insular point through the anterior periinsular sulcus. Ventro-laterally, we stopped at the level of the anterior transverse insular gyrus to draw the anterior short gyrus; ventromedially, we stopped at the level of the junction between the internal and external capsule. We continued from there ventrocaudally toward the limen insula (at the limit of the temporal operculum) and the inferior periinsular sulcus, stopping at the posterior insular point caudally to draw the posterior long gyrus. We then segmented dorso-caudally from there at the limit of the superior periinsular to finish at the anterior insular point closing the superior part of the insula. We then separated the insula into an anterior and posterior region as delimited by the insular central sulcus. From an axial view, we started medially at the inferior periinsular sulcus, caudally, to

the short insular sulcus, dorsally, passing at the junction of the external capsule and stopping laterally at the limit of the CSF in the Sylvian fissure. Finally, centroids were regularly placed within each gyri and then simultaneously inflated, resulting in a parcellation into 19 regions (Figs 2a and b). The same technique was used for both hemispheres; the visible differences in each ROIs may be the result of interhemispheric differences. The voronoï-partitioning algorithm of the cortex and the number of insular ROIs was inspired from previous studies (Hagmann et al. 2007, 2008; Zalesky et al. 2010).

[FIGURE 1a & 1b]

[FIGURE 2a & 2b]

HARDI data preprocessing

The preprocessing steps described in this paragraph have been done on each subject separately. We first applied eddy current correction from FSL Diffusion Toolbox (FDT) to adjust the diffusion data for distortion and motion using affine registration to the non-weighted diffusion volume (b = 0 s/mm2). We then applied a nonlocal means (NL-means) Rician denoising method on all diffusion-weighted volumes to increase image quality (Coupe et al. 2008). The resulting image was upsampled to a 1mmresolution to better differentiate the insula, the claustrum, and the extreme capsule, as done in other HARDI tractography work (Raffelt et al. 2012; Smith et al. 2012; Girard et al. 2014). We performed a quality assurance on the resulting images by verifying the T1-weighted white-matter mask and the red-green-blue (RGB) diffusion color map. Using BET from FSL on the b = 0 image, we extracted the brain and created a binary brain mask so the preprocessing on diffusion images is performed

only on the brain. Diffusion tensors (Basser et al. 1994) and a fractional anisotropy (FA) map were created using MRtrix package (J-D Tournier, Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/, last accessed November 27, 2015; Tournier et al. 2012). The FA map is used for verification purposes (Tournier et al. 2007) as the data are visually checked after each step. We use a white-matter probabilistic map, obtained from anatomical T1-weighted image, in the tracking algorithm as it has been shown to produce richer and more accurate streamlines than a thresholded FA map (Girard et al. 2014). The coregistration between the T1-weighted image and the resampled to 1-mm diffusion images was performed using ANTS affine registration (Avants et al. 2011). The ROIs of the cortex and the insula were then resampled to every single-subject diffusion space. To check the validity of the registration from the template to individual diffusion space, we manually segmented 5 random subjects following the boundaries previously described and used 2 overlap agreement measures described in Klein et al. (2009) to compare the templates segmentation with these 5 subjects. We obtained an overlap of 82% and 86% for the "target overlap" and the "dice coefficient," respectively (Dice 1945). Constrained spherical deconvolution (CSD) (Tournier et al. 2007; Descoteaux et al. 2009) computation was performed using MRtrix (Tournier et al. 2012) to resolve crossing-fibers more effectively while supporting more effectively noise effects (Tournier et al. 2008). Thereby, streamline tracking was launched on resulted fiber orientation distribution functions (fODF) (Tournier et al. 2007; Descoteaux et al. 2009) using a deterministic tractography algorithm (Girard et al. 2014) with a threshold of 150 seeds per voxel from all 19 ROIs of the insula and 200 ROIs of the cortex in both hemispheres. Because tractography cannot determine the orientation of a fiber, whether it is afferent or efferent, and because the path and angle of the tracts will differ

depending on its starting point, we launched the tractography algorithm from both the insula and the cortex. After running the tractography algorithm on 5 random subjects with different thresholds ranging from 1 to 10 000 seeds per voxel, we observed a plateau of ~6000 streamlines with 300–400 seeds per voxels. Taking into consideration the computational power and time required for analysis, we elected to choose a threshold of 150 seeds per voxel which provided us with at least 5000 streamlines for every ROIs (very close to the plateau of 6000 streamlines). We used the probabilistic subject's GM map as an inclusion parameter, and the CSF and non-brain voxels as an exclusion parameter; the step size was 0.5 mm; as described in Girard et al. (2014).

Normalization

To account for the difference in size of the ROIs, we normalized connectivity values relatively to the biggest ROI. Then, because tractography algorithm is not bijective, we summed each connection with its inverse for a better estimation of the real connectivity between each pair of ROIs.

Visualization

The template representing the 46 T1-weighted images, the 19 insula ROIs of each hemisphere, and the cortex ROIs were affine aligned to the Montreal Neurological Institute (MNI) 152 standard space. The regions were identified using the following FSLview integrated atlases: Harvard-Oxford cortical structural atlas (Frazier et al. 2005; Desikan et al. 2006; Makris et al. 2006; Goldstein et al. 2007), the MNI structural atlas (Collins et al. 1995; Mazziotta et al. 2001), and an atlas based on functional correlations (Tamraz et al. 2004).

Results

Connectivity profile of the insula

Bijective cortical connections of the 19 insular ROIs, with a threshold of 150 streamlines per voxel, are reported in Table 1 (for the left hemisphere) and Table 2 (for the right hemisphere). These results are also illustrated in Figure 3a (left hemisphere) and b (right hemisphere) and a general tractography illustration on one random subject is shown in Figure 4 for schematic purposes. Furthermore, in order to obtain a broadband connectivity map of the insula, we created a supplementary figure reflecting the connections ranging from 50 to 500 streamlines per voxel (Fig. 5a for the left hemisphere and b for the right hemisphere). As can be seen, the insula shows connections with the frontal, parietal, temporal, and occipital lobes, and limbic areas.

[FIGURES 3a & 3b]

[TABLE 1 & 2]

Widespread connections are observed between the insula and the frontal lobe. Insular ROIs from both hemispheres are connected with the inferior, including pars triangularis and orbitalis (Broca's area), middle, and superior frontal gyri, orbitofrontal cortex, precentral gyrus, frontal operculum, and subcallosal gyrus. With regards to the temporal lobe, the insula has connections with the superior temporal gyrus including Heschl's gyrus (auditory cortex), the planum temporale (Wernicke's area and associative auditory cortex), the planum polare, the temporal fusiform gyrus, and the temporal operculum. Within the parietal lobe, the insula has connections with the supramarginal and angular gyri, the precuneus and the superior

parietal lobule, as well as the postcentral gyrus (somatosensory cortex; BA 1, 2, 3) and the parietal operculum. Within the occipital lobe, the insula has connections with the cuneus and lingual gyri, occipital fusiform gyrus, while including the lateral occipital cortex. Within limbic areas, the insula has connections with the parahippocampal gyrus, including the uncus, perirhinal and entorhinal cortices, and the anterior and posterior cingulate gyrus. More precisely, we report fibers connecting the anterior regions of the insula with the anterior cingulate cortex (BA 24), the anterior midcingulate cortex (BA 24, 32, 33), the subgenual subregion (BA 25), and the perigenual anterior cingulate cortex (BA 24, 32), while posterior regions of the insula are connected with the dorsal posterior cingulate cortex (BA 31) and the posterior midcingulate cortex (BA24, 33). We also found connections between the insula and the parahippocampal gyrus (anterior and posterior regions) including the entorhinal (BA28, 34) and perirhinal cortices (BA 35, 36), as well as the Uncus (BA 28). Most of the reported regions with a threshold of 150 streamlines per voxels are still present with a higher threshold (up to 500, in yellow) (Fig. 4a and b). Indeed, many key regions are still connected in both hemispheres, including the superior and inferior temporal gyri, the anterior and posterior cingulate gyri, the precentral, postcentral, supramarginal, and angular gyri, the orbitofrontal as well as the occipital cortices. We also observe a rostro-caudal like connectivity pattern as rostro-dorsal anterior ROIs are mainly connected to frontal and temporal lobes while ventro-caudal posterior like ROIs are mostly connected to temporal, parietal and occipital lobes (see Table 3).

[TABLE 3]

Discussion

Our work reveals a wide array of connections between the insula and the frontal, temporal, and parietal lobes, and limbic areas, in agreement with tracing studies in macaques (Pandya et al. 1981; Mesulam and Mufson 1982a,b; Mufson and Mesulam 1982; Vogt and Pandya 1987; Vogt et al. 1987), structural (Cerliani et al. 2012; Cloutman et al. 2012; Jakab et al. 2012), and resting-state functional magnetic resonance imaging (rsfMRI) (Mutschler et al. 2009; Taylor et al. 2009; Van Den Heuvel et al. 2009; Cauda et al. 2011; Deen et al. 2011) studies in humans. Notably, the insula showed connections with the orbitofrontal cortex, supplementary motor area, frontal operculum, the primary motor and the somatosensory cortices, the parietal operculum, the auditory cortex, the prorhinal and entorhinal cortices (part of the anterior parahippocampal gyrus). This connectivity profile remains relatively stable by moving the standard threshold of 150 seeds per voxel to a more robust threshold of 500. A clear differential connectivity pattern, moving from a ventral anterior to a dorsal posterior organization, was observed. Remarkably, we were also able to reveal for the first time in humans clear structural connectivity between the insular cortex and cingulate cortex as well as the parahippocampal, angular, supramarginal, precuneus, cuneus, lingual and the fusiform gyri by overcoming known methodological limitations such as crossing-fibers (i.e., corona radiata) (Dougherty et al. 2005), and invalid connections (i.e., DTI-based probabilistic approach) (Yo et al. 2009). We suggest that we overcame, to some degree, crossing-fibers limitations by using high resolution data (1 mm) and HARDI with fODF compared with standard DTI tractography (2 mm) (Descoteaux et al. 2009; Jones et al. 2013; Kuhnt et al. 2013). Indeed, using anatomical priors results in having more valid connections and less invalid connections that end prematurely in the WM or stop in ventricles and does not connect cortical or

subcortical areas. The particle filtering tractography algorithm also allows better propagation in narrow and tight white-matter band, which can be important in the complex areas surrounding the insula (Girard et al. 2014). Because of these methodological steps to minimize stray streamlines and artifacts, we surmise that obtained images represent actual connections. The fact that observed connections (e.g. cingulate, angular, supramarginal, lingual and parahippocampal gyri as well as precuneus and occipital cortex) are very much in line with cumulative data from tract-tracing studies in macaques (Mesulam and Mufson 1982b; Mufson and Mesulam 1982), functional studies in humans (Mutschler et al. 2009; Taylor et al. 2009; Van Den Heuvel et al. 2009; Cauda et al. 2011; Deen et al. 2011), and the limited number of tractography studies of the human insula (Cerliani et al. 2012; Cloutman et al. 2012; Jakab et al. 2012) is reassuring. As for the parahippocampal gyrus, its structural connectivity is poorly known and only a few studies have reported connections with the insula in rhesus monkeys and rats (Room and Groenewegen 1986; Insausti et al. 1987; Blatt et al. 2003; Kerr et al. 2007). One can speculate that the failure to observe the connectivity between the insula and the parahippocampal gyrus may be a result of the same limitations that apply for the cingulate cortex considering that it is part of a subcortical region encompassing a multitude of white-matter tracts (i.e., cingulum) (Catani and Thiebaut de Schotten 2008).

Cingulate Cortex

Although prior structural studies in humans have not revealed connections between the insula and cingulate cortex, a wide range of functional studies using rsfMRI have reported simultaneous activation of these 2 regions (Taylor et al. 2009; Van Den Heuvel et al. 2009; Cauda et al. 2011; Deen et al. 2011; Chang et al. 2013).Here,we show that there is indeed a

direct connection between the insula and the cingulate cortex and that their functional co-activation, previously reported by rsfMRI, is a reflection of this direct link. In addition, the revealing of the antero-posterior pattern of structural connectivity between both structures is also in line with functional connectivity patterns reported in earlier rsfMRI studies: While the anterior insula is mainly connected with the anterior cingulate cortex, the posterior insula is preferentially connected with the posterior cingulate cortex (Cauda et al. 2011; Cerliani et al. 2012; Cloutman et al. 2012; Jakab et al. 2012). This strong link between both structures is further supported by the fact that their shared organization type (Vogt et al. 1995; Eickhoff et al. 2010), their neurons, such as VENs (Nimchinsky et al. 1995; Allman et al. 2011; Butti et al. 2013), and their shared functions (Torta and Cauda 2011).

Occipital Lobe

In accordance with previous structural (Cloutman et al. 2012; Jakab et al. 2012) and functional studies (Menon and Uddin 2010; Uddin et al. 2010; Cauda et al. 2011), we also report connections with the occipital lobe. An occipital connection might be plausible in pair with the claustrum due to their proximity (for a review, see Mathur 2014) along the external capsule, the uncinate fascicles, the corona radiata (Nieuwenhuys et al. 1988; Fernández-Miranda et al. 2008), or the inferior fronto-occipital fasciculus (IFOF) (Martino et al. 2010). Indeed, the claustrum and the parieto-occipital regions have been reported to have direct connections in animals (Mesulam and Mufson 1982b; Shipp et al. 1998; Tanné-Gariépy et al. 2002; Crick and Koch 2005) and humans (Schmahmann and Pandya n.d.; Schmahmann et al. 2007; Catani and Thiebaut de Schotten 2008). In addition, the IFOF, which is reported to be

located underneath the insula and may be involved in the semantic system, has been shown to have connections with the temporal, parietal, and occipital lobes (Martino et al. 2010).

Related insular functions

The widespread connections found between the insula and other cortical regions are consistent with the wide range of brain functions associated with this structure and with the variety of neuropsychological impairments reported in patients with isolated insular damage. Insular connections with the frontal lobe are congruent, among others, with an insular involvement in language processes including speech initiation and complex articulation (Dronkers 1996; Bates et al. 2003; Boucher et al. 2015), and with high-order executive processes involving an affective component, such as risky decision-making (Clark et al. 2008; Weller et al. 2009). Connections with auditory areas in the temporal lobe might explain the variety of central auditory deficits observed in patients with isolated insular damage (Bamiou et al. 2006), whereas those with parietal areas may be responsible for the hemispatial neglect and impaired body scheme representation described in some patients (Manes et al. 1999; Karnath et al. 2005; Golay et al. 2008). The insula and cingulate cortex have also been associated with similar neuropsychological functions, including self-awareness and representation of time and space, empathy, pain, and social behavior (Torta and Cauda 2011; Cauda et al. 2013, 2014), as well as being part of a salience or frontoparietal network (Seeley et al. 2007; Vincent et al. 2008; Menon and Uddin 2010). Similarly, the precuneus (Cavanna and Trimble 2006; Cabanis et al. 2013) and the supramarginal gyrus have been reported to be implicated in empathy and self-awareness. Finally, insular-occipital connections (cuneus and lingual gyrus), although somewhat less consistent with the literature, might be consistent with

the impairment in facial emotional expression recognition following insular damage (Dal Monte et al. 2013) and may also be supported by functional studies on illusory own-body perception and self-perception, as well as word recognition among others (Karnath and Baier 2010; Craig 2011; Chiarello et al. 2013; Heydrich and Blanke 2013).

The insula seems to be part of the salience network (SN), which is formed by the dorsal anterior cingulate cortex (dACC) and the insular cortex with robust connectivity to subcortical and limbic structures (Seeley et al. 2007; Cauda et al. 2012; Ham et al. 2013). It has also been suggested that the 2 insular cortices have different patterns of functional connectivity. The anterior part of the SN is right sided and has stronger connections with the right AIC, right ACC, and many subcortical structures such as the brainstem, pons, and thalamus. The posterior part, which is the visuomotor integration network, has mild right sided connections with the superior temporal cortex and the occipital cortex (Cauda et al. 2011).

Limitations

The major limitation in our study is of technical nature, related to the diffusion-weighted imaging (DWI) tractography itself. While problems ensuing from false-negatives and crossing-fibers are reduced when using HARDI and CSD, we cannot completely exclude that some of the connecting fibers identified were crossing-fibers unrelated to the insula. As shown in Côté et al. (2013), probabilistic tracking with a large number of seeds produces a lot more invalid connections than corresponding HARDI deterministic tracking. Since the insula is a complex structure with a large number of crossing-fibers, we preferred to stay more conservative and use a deterministic tracking algorithm. In addition, typical DWI limitations persist in our study. These include the lack of standard criterion (i.e., threshold value and

streamlines number) (for a review, see Dell'Acqua and Catani 2012), and a persistent low spatial resolution (even at 1 × 1 × 1 mm) of the claustrum, as well as the distance effect (Morris et al. 2008). Furthermore, it cannot distinguish between afferent and efferent projections unlike tract-tracing injection (Johansen-Berg and Behrens 2006), posing a significant challenge to finding intra-connections of the insula. Moreover, diffusion tractography analysis cannot be run on the template image; therefore, any registration method from the template to the subject's space has its own methodological limitation. For example, the b0 to T1 registration can result in slight mislocation of anatomy due to distortions. Indeed, because of MRI resolution limitations, it is possible that a few voxels of ventro-posterior ROIs of the insula include parts of the claustrum and that a few voxels of ventro-rostral anterior ROIs of the insula include parts of the orbitofrontal cortex.

Lastly, the atlases used to extract the connected regions are limited by their lack of standardized nomenclature and the omission of some regions.

Conclusion

Contrary to the current tractography-based connectivity of the insula literature, our work is based on a larger sample (n = 46) and uses the latest state-of-the-art HARDI tractography based on anatomical priors as described in the methodology. Our results show novel and clear connections between the insula and the cingulate, fusiform, parahippocampal, angular and supramarginal gyri as well as the precuneus and to a lesser extent with the cuneus and lingual gyrus. Hence, our results provide a structural basis to fundamental functions such as pain, empathy, emotion, face recognition, interoception, language, social behavior, etc. Considering the brain is organized like a "small-world" network (Bianchi et al. 2012), these

results help to further the understanding of the functional role the insula plays as a multimodal structure. Moreover, the continuous improvements of tractography techniques may help further investigate subcortical regions such as the hippocampus, the amygdala, the thalamus, and the striatum, providing the opportunity to compare structural interhemispheric connectivity. Consequently, a comparative study with clinical patients might also be beneficial.

Acknowledgements

The authors would like to thank the following persons for sharing the data with us: Dr. Mario Beauregard, Ph.D. (Montreal) and Dr. Sarah Lippe, Ph.D. (Montreal), and the staff of the Neuroimaging Unit at the Centre de recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM, Hôpital Notre-Dame) for their technical assistance.

In memory of Jean-Maxime Leroux.

Conflict of interests: The authors declare no conflicts of interest.

Funding

This study was supported by Quebec Bio-Imaging Network (RBIQ/QBIN) # 4.11.

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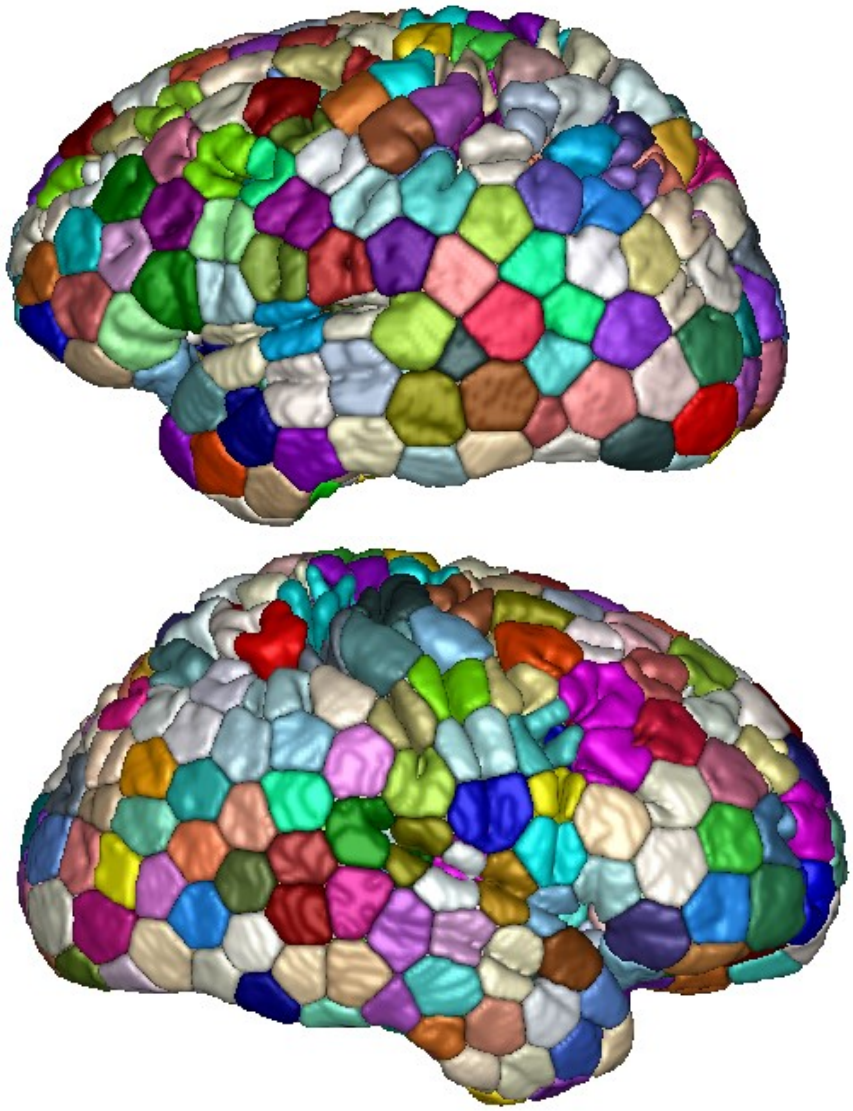

Figure 1. (a) Random parcellation of the left cortex into 200 regions (voronoï). (b) Random parcellation of the right cortex into 200 regions (voronoï).

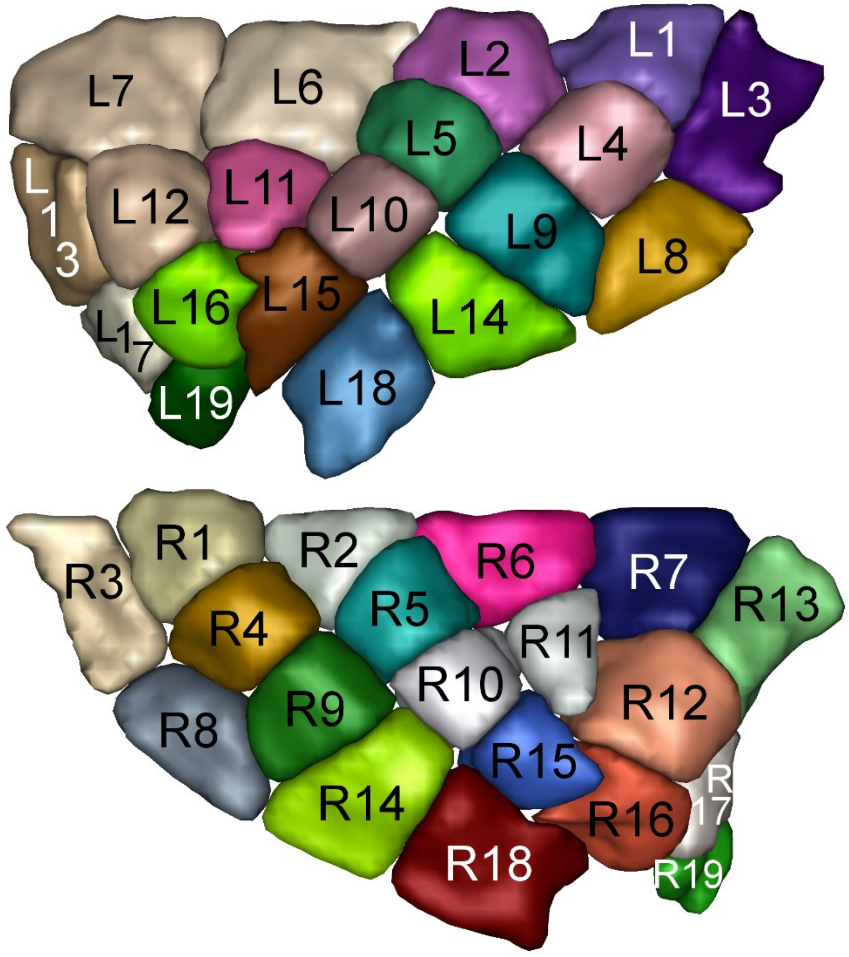

Figure 2. (a) Random parcellation of the left insula into 19 regions (voronoï). (b) Random parcellation of the right insula into 19 regions (voronoï).

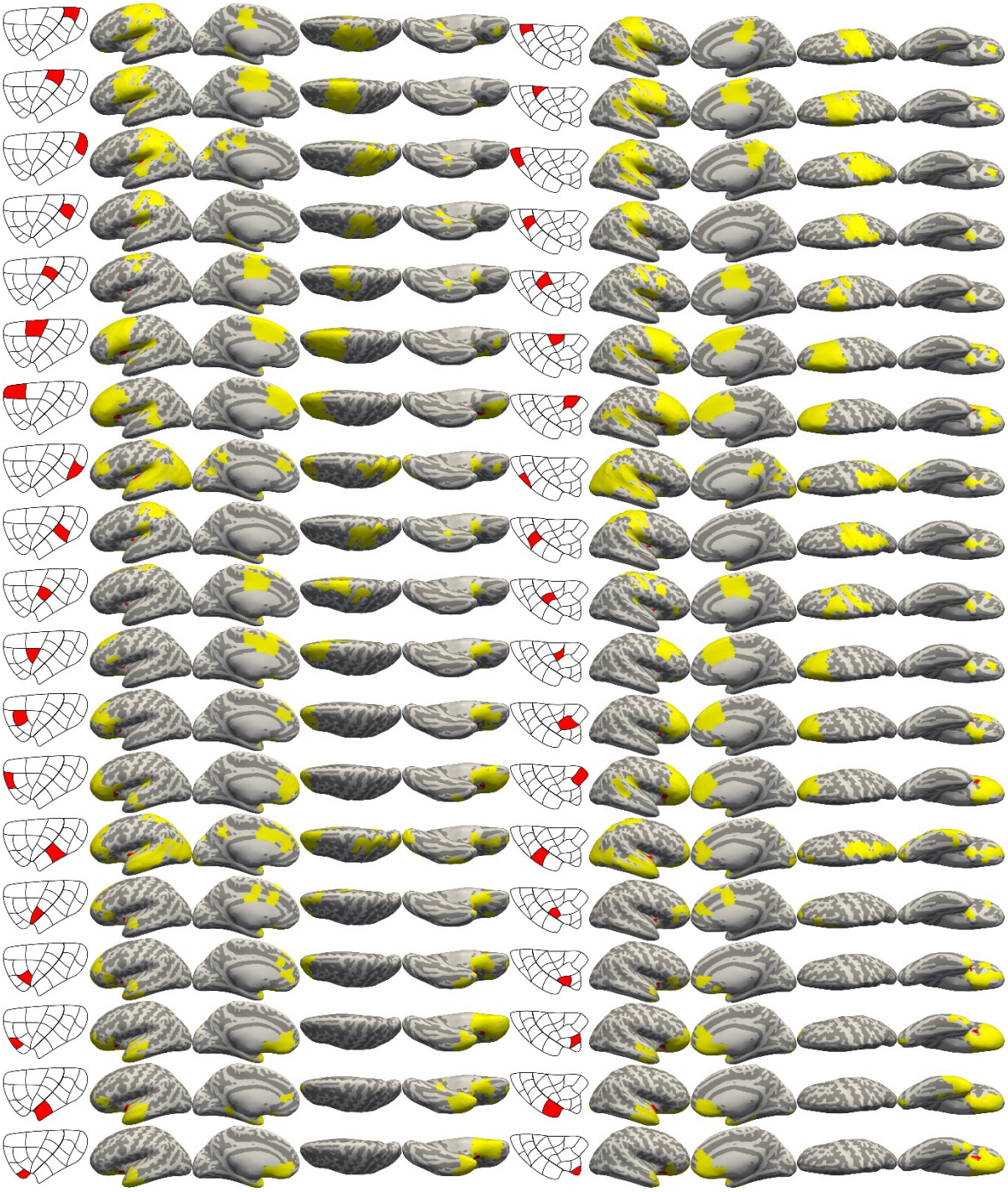

Figure 3. (a) Connectivity between the left insula and cortical ROIs with a threshold of 150 tracts per voxel. (b) Connectivity between the right insula and cortical ROIs with a threshold of 150 tracts per voxel.

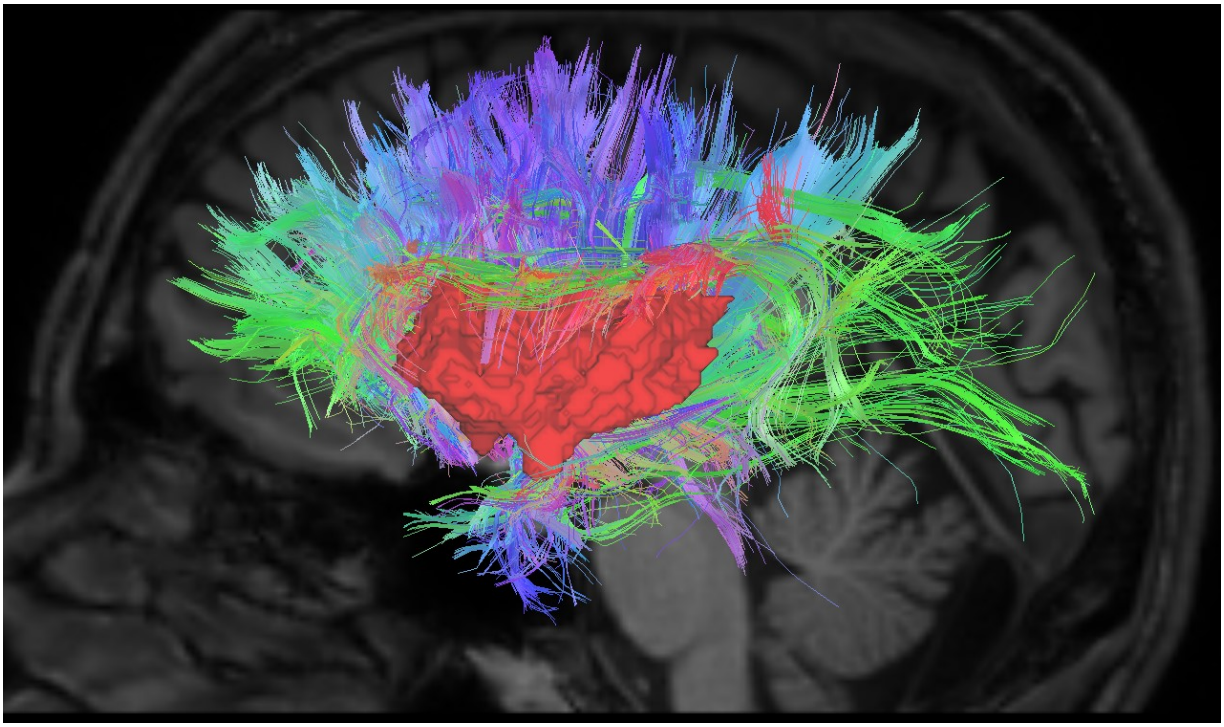

Figure 4. Streamlines from the insula to the cortex on a random subject with a threshold of 150 streamlines per voxel for illustrative purposes. Colors: Red: left-right; green: back-front; blue: up-down.

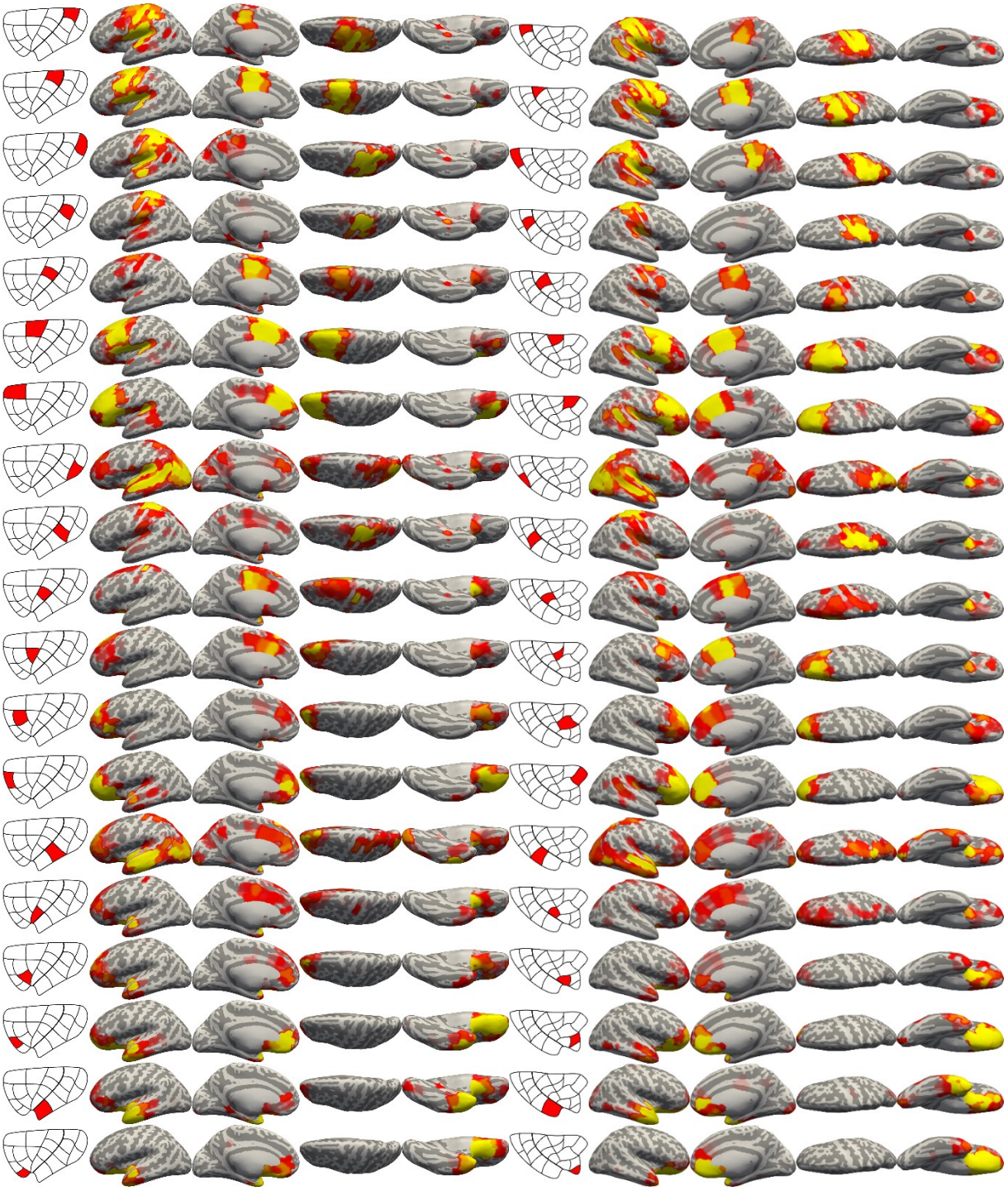

Figure 5. (a) Connectivity between the left insula and cortical ROIs with a threshold ranging from 50 (red), 150 (orange) to 500 (yellow) tracts per voxel. (b) Connectivity between the right insula and cortical ROIs with a threshold ranging from 50 (red), 150 (orange) to 500 (yellow) tracts per voxel.

Regions	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19
Frontal lobe																			
		X			X	X	X	X		X	X	X	X	X	X	X			
Superior frontal gyrus	X																		
Middle frontal gyrus	X	X			X	X	X	X			X	X		X					
Inferior frontal gyrus						X	X	X			X								
Orbital frontal cortex	X				X	X	X	X	X		X	X	X	X	X	X	X	X	X
Pars triangularis						X	X	X			X	X	X	X	X	X		X	
Pars opercularis		X				X	X	X			X	X							
Precentral gyrus	X	X	X	X	X	X	X	X	X	X				X					
Frontal opercula	X	X				X	X					X	X		X	X	X	X	
Frontal pole	X					X	X	X			X	X	X	X	X	X	X	X	
Parietal lobe																			
			X	X				X	X					X					
Superior parietal lobule	X																		
Postcentral gyrus	X	X	X	X	X			X	X					X					
Supramarginal gyrus	X	X	X	X		X	X	X	X					X					
Angular gyrus			X					X						X					
Parietal opercula	X	X	X	X		X	X	X	X				X	X					
Precuneus			X					X						X					
Temporal lobe																			
		X	X			X	X	X					X	X	X	X	X	X	X
Superior temporal gyrus	X																		
Planum temporale	X	X	X	X		X	X	X	X				X	X					
Planum polare	X	X	X			X		X	X	X			X	X	X	X	X	X	X
Heschl's gyrus	X	X	X	X		X	X	X	X					X			X	X	
Middle temporal gyrus	X		X				X	X					X	X	X	X	X	X	X
Inferior temporal gyrus							X						X	X		X	X	X	X
Temporal fusiform gyrus	X		X	X													X	X	X
Temporal pole		X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Occipital lobe																			
			X					X	X					X					
Lateral occipital cortex																			
Cuneus			X																
Lingual				X														X	
Occipital fusiform gyrus																			
Occipital pole								X						X					
Limbic regions																			
					X				X	X		X			X	X	X	X	X
Anterior parahippocampal gyrus																			
Posterior parahippocampal gyrus	X		X	X	X				X										
Anterior cingulate gyrus	X	X			X	X	X	X		X	X	X	X	X	X	X	X	X	X
Posterior cingulate gyrus		X	X											X					

Table 1. Connectivity between the ROIs of the left insula and the left ROIs of the cortex with a threshold of 150 fibers per voxel**.**

Regions	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16	R17	R18	R19
Frontal lobe																			
Superior frontal gyrus		X			X	X	X	X		X	X	X	X	X	X				
Middle frontal gyrus		X			X	X	X			X	X	X	X						
Inferior frontal gyrus		X				X	X	X			X	X	X		X	X	X		
Orbital frontal cortex	X	X	X			X	X		X	X	X	X	X	X	X	X	X	X	X
Pars triangularis						X	X					X	X		X	X	X		
Pars opercularis		X				X	X	X			X	X	X						
Precentral gyrus	X	X	X	X	X	X	X	X	X	X				X					
Frontal opercula		X				X	X					X				X	X		
Frontal pole	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X
Parietal lobe				X				X	X					X					
Superior parietal lobule	X																		
Postcentral gyrus	X	X	X	X	X			X	X	X				X					
Supramarginal gyrus	X	X	X	X			X	X	X				X						
Angular gyrus	X	X				X	X	X	X				X	X					
Parietal opercula	X	X	X	X	X	X	X	X	X	X			X						
Precuneus			X					X											
Temporal lobe		X	X		X	X	X							X		X	X	X	X
Superior temporal gyrus	X																		
Planum temporale	X	X	X	X	X	X	X	X	X	X			X						
Planum polare		X	X		X	X		X						X		X	X	X	X
Heschl's gyrus	X	X	X	X	X	X	X	X	X	X			X	X					
Middle temporal gyrus	X	X	X				X	X						X			X	X	X
Inferior temporal gyrus														X		X	X	X	X
Temporal fusiform gyrus														X		X		X	X
Temporal pole						X		X	X				X	X		X	X	X	X
Occipital lobe			X	X			X	X	X					X					
Lateral occipital cortex																			
Cuneus								X											
Lingual																	X	X	
Occipital fusiform gyrus								X						X				X	
Occipital pole								X						X			X	X	
Limbic regions		X		X										X				X	
Anterior parahippocampal gyrus																			
Posterior parahippocampal gyrus																			
Anterior cingulate gyrus		X			X	X	X			X	X	X	X	X	X	X	X	X	X
Posterior cingulate gyrus	X	X	X					X											

Table 2. Connectivity between the ROIs of the right insula and the right ROIs of the cortex with a threshold of 150 fibers per voxel

ROIs	Directionality	Lobes	Rois	Directionality	Lobes
L1	Dorsal Posterior	Frontal, temporal and parietal	**R1**	Dorsal Posterior	Frontal, temporal and parietal
L2	Dorsal Posterior	Frontal and temporal	**R2**	Dorsal Posterior	Frontal, temporal and parietal
L3	Dorsal Posterior	Temporal, parietal and occipital	**R3**	Dorsal Posterior	Frontal, temporal, parietal and occipital
L4	Dorsal Posterior	Temporal and parietal	**R4**	Dorsal Posterior	Frontal, temporal, parietal and occipital
L5	Dorsal Anterior	Frontal	**R5**	Dorsal Anterior	Frontal, temporal and parietal
L6	Dorsal Anterior	Frontal and temporal	**R6**	Dorsal Anterior	Frontal, temporal and parietal
L7	Dorsal Anterior	Frontal and temporal	**R7**	Dorsal Anterior	Frontal, temporal, parietal and occipital
L8	Dorsal Posterior	Frontal, temporal, parietal and occipital	**R8**	Dorsal Posterior	Frontal, temporal, parietal and occipital
L9	Dorsal Posterior	Frontal and temporal	**R9**	Dorsal Posterior	Frontal, temporal, parietal and occipital
L10	Dorsal Anterior	Frontal and parietal	**R10**	Dorsal Anterior	Frontal, temporal and parietal
L11	Dorsal Anterior	Frontal	**R11**	Dorsal Anterior	Frontal
L12	Dorsal Anterior	Frontal	**R12**	Dorsal Anterior	Frontal
L13	Dorsal Anterior	Frontal and temporal	**R13**	Dorsal Anterior	Frontal, temporal and parietal
L14	Ventral Posterior	Frontal, temporal, parietal and occipital	**R14**	Ventral Posterior	Frontal, temporal, parietal and occipital
L15	Ventral Anterior	Frontal and temporal	**R15**	Ventral Anterior	Frontal
L16	Ventral Anterior	Frontal and temporal	**R16**	Ventral Anterior	Frontal and temporal
L17	Ventral Anterior	Frontal and temporal	**R17**	Ventral Anterior	Frontal, temporal and occipital
L18	Ventral Posterior	Frontal and temporal	**R18**	Ventral Posterior	Frontal, temporal and occipital
L19	Ventral Anterior	Frontal and temporal	**R19**	Ventral Anterior	Frontal and temporal

Table 3. Rostro-caudal connectivity pattern of the left and right hemispheres

Discussion

L'objectif principal de ce mémoire consistait à étudier la connectivité structurelle de l'insula chez l'humain par tractographie en utilisant les méthodes les plus avancées disponibles dans le domaine sur un nombre significatif de sujets. Après avoir présenté brièvement l'anatomie, les fonctions et la connectivité de l'insula chez les macaques, nous avons donné un aperçu des méthodes en neuro-imagerie (IRMf, IRMfer et l'imagerie de diffusion), afin de mieux cerner leurs limites respectives. Cette description a éclairé les difficultés auxquelles ont longtemps fait face les chercheurs et illustre les capacités des dernières avancées méthodologiques en algorithme de tractographie.

L'étude publiée (Ghaziri et al., 2015) a permis de révéler pour la première fois des connexions structurelles claires entre l'insula et les gyri cingulaire antérieur et postérieur, supramarginal, angulaire, fusiforme et parahippocampique (incluant périrhinal et entorhinal), le cortex occipital incluant le cunéus, le gyrus lingual et le cortex occipital latéral ainsi que le précunéus. Ces résultats furent possibles grâce à l'utilisation d'outils et d'algorithmes d'analyse avancés et adaptés à ce type d'étude afin de surpasser, dans la mesure du possible, les limites méthodologiques des calculs et estimations de la tractographie, face aux croisements de fibres, et ce, en utilisant un échantillon plus important que les études précédentes (N = 46). Ces résultats peuvent servir de base comparative pour les études fonctionnelles et permettent de mieux illustrer les rôles que joue l'insula en tant que structure multimodale. De plus, ils s'enlignent avec l'hypothèse du rôle intégratif sur les différents réseaux cérébraux que joue l'insula dans le traitement des modalités sensorielles (p. ex.

audition, odorat), des émotions (p. ex. douleur, empathie), dans les tâches cognitives (p. ex. attention, mémoire) ou dans les psychopathologies (p. ex. anxiété), par ses connexions avec les cortex frontal, orbitofrontal, pariétal et cingulaire, l'amygdale et l'hippocampe.

Limites de l'étude

Malgré ces nouvelles découvertes, cette étude comporte certaines lacunes méthodologiques. Tel que mentionné dans l'introduction, l'IRM est la principale lacune, notamment en raison de la faible résolution de l'image, la sensibilité aux mouvements ainsi que l'incapacité à différentier la direction des fibres de matière blanche. De plus, il ne faut pas négliger l'ampleur du pré-traitement des données par l'utilisation de différents logiciels spécialisés, le développement d'algorithmes ou de scripts maison, qui tous peuvent influencer les résultats finaux. Ce type de pré-traitement polymorphe peut causer des incompatibilités, des interférences ou influencer les résultats (p. ex. l'interaction entre différents logiciels, l'extraction du crâne, la segmentation des tissus cérébraux, le lissage et la normalisation des données) tout au long des étapes, pouvant accroître ainsi les risques de faux négatifs et de faux positifs. Ces variables, qui sont parfois omises, peuvent par la suite avoir un important impact sur les résultats finaux de l'image initialement acquise. La connectivité intra-insulaire ou entre l'insula et le claustrum par exemple serait des cas exceptionnellement difficiles à étudier par IRM considérant la proximité spatiale de ces régions, mais aussi en raison d'une faible résolution et ce, même à 1mm.

Concernant les statistiques, la principale lacune serait le manque de comparaisons inter-individuelles afin de valider l'effet de groupe ainsi que la prise en compte de la variabilité inter- et intra-individuelle dans l'analyse des données. Ceci pourrait se faire, par exemple, en divisant l'échantillon en deux groupes de même taille et de comparer ceux-ci afin d'évaluer la fidélité de la reproduction des résultats. Malheureusement, ce type d'analyse, étant donné la quantité et la qualité des données, serait d'une grande lourdeur tant sur le plan du stockage et des ressources informatiques, que sur celui du temps d'analyse.

Perspectives futures de recherche

D'autres avenues sont en cours d'exploration afin d'éclairer davantage les connectivités fonctionnelle et structurelle ainsi que leurs relations.

Par sa complexité, l'insula est souvent étudiée selon la fonction neuropsychologique spécifique qui intéresse le chercheur, alors qu'il existe très peu d'études faisant le lien entre l'activité fonctionnelle, la connectivité structurelle, les fonctions et la région insulaire spécialisée. Ce décorticage du profil général doit se faire en plusieurs étapes. En premier lieu, il serait important d'établir une référence du profil des connexions structurelles entre l'insula, le cortex et les régions sous-corticales. Cette étape est cruciale pour la comparaison des données fonctionnelles afin de corroborer le profil de connectivité, mais plus précisément, les fonctions qui peuvent être reliées à l'insula. En deuxième lieu, une recension des données fonctionnelles, tant chez des sujets normaux que chez des patients atteints de maladies neurologiques (p. ex. épilepsie) ou psychiatriques (p. ex. schizophrénie, trouble de l'anxiété),

de troubles du développement (p. ex. autisme) ou de psychopathologies (p. ex. dépendance), permettrait d'obtenir un profil des fonctions qui activent l'insula, mais également de clarifier s'il y a présence de sous-spécialisation insulaire (p. ex. latéralisation et sous-division). En troisième lieu, en nous basant sur l'analyse des données des deux premières étapes (c.-à-d. les connexions structurelles et fonctionnelles), nous pourrions établir une division de l'insula en régions fonctionnellement spécialisées. Ainsi, l'ensemble de ces étapes permettrait d'enrichir nos connaissances sur les fonctions qui seraient directement reliées à l'insula, mais aussi de différencier celles qui y sont reliées par une tierce région à proximité. Par exemple, la proximité de l'insula et du claustrum ou de l'insula et du faisceau arqué avec les aires de Broca et de Wernicke. Finalement, les connaissances acquises seraient une occasion idéale de réaliser des études cliniques comparatives sur des patients ayant subi un AVC, un traumatisme crânien ou atteints d'épilepsie.

Connectivité structurelle sous-corticale de l'insula chez l'humain

Seules les études par traçage chez les primates non humains rapportent des connexions claires entre l'insula et les régions sous-corticales (Mesulam & Mufson, 1982a, 1982b; Mufson & Mesulam, 1982). Les quelques études chez l'humain, à l'aide de l'imagerie de diffusion, ont brièvement rapporté de possibles connexions avec le thalamus, l'amygdale et le putamen (Cerliani et al., 2012; Cloutman et al., 2012; Jakab et al., 2012). Notre équipe a entrepris l'analyse des régions sous-corticales telles que le thalamus, l'hippocampe, l'amygdale, le putamen, le globus pallidus, le noyau caudé et les noyaux accumbens (Figure 1); une suite logique de l'étude présentée dans cet ouvrage. Il va sans dire que la

méthodologie diffère, du fait que les régions étudiées sont profondes, et donc plus propices aux faux négatifs dus à l'augmentation des croisements de fibres. De surcroit, les fibres étant très denses dans les régions profondes, les méthodes d'investigation sont encore élémentaires, mais semblent prometteuses. En effet, notre équipe vient d'étudier la connectivité sous-corticale de l'insula chez l'humain et les résultats préliminaires rapportent une connexion entre l'insula et toutes les sept régions sous-corticales nommées plus haut. Certaines lacunes méthodologiques ont fait surface et nous travaillons actuellement à y remédier, dans la mesure du possible, avant de soumettre un premier manuscrit.

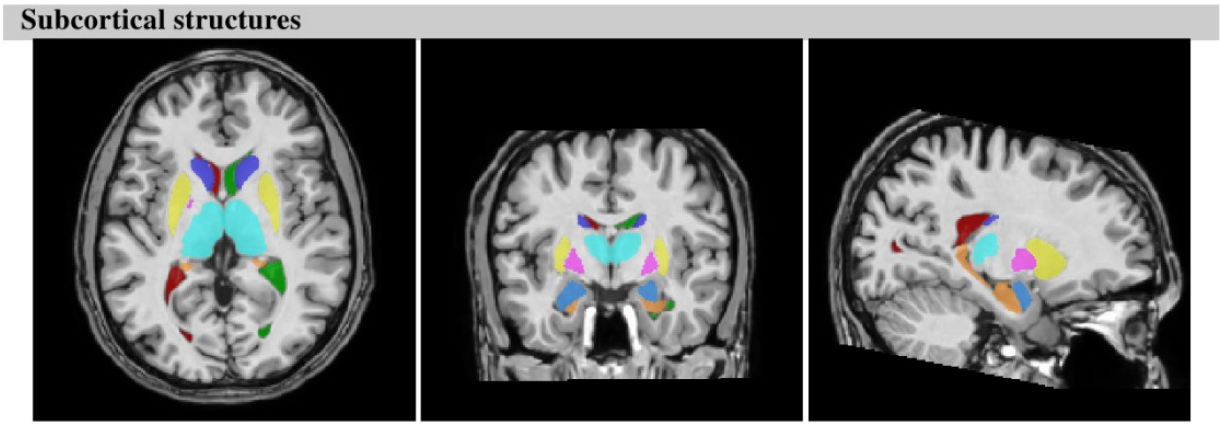

Figure 1. Illustration des régions sous-corticales.

Profil de connectivité insulaire chez l'humain

En plus de l'intérêt que notre équipe porte à la connectivité structurelle, nous nous intéressons également à l'IRMfer dans le but de déceler les réseaux corticaux et sous-corticaux auxquels feraient partie l'insula. Pour ce faire, nous avons recruté 50 sujets sains sans antécédents neurologiques ou psychiatriques afin de passer une IRMfer et une IRM de diffusion en utilisant une antenne à 32 canaux, plutôt que 8 dans l'étude actuelle. Le premier

objectif de cette étude est de déceler les réseaux impliquant l'insula, puis de corroborer ceux-ci avec les connexions structurelles obtenues avec l'antenne à haute définition (Figure 2). Cela concerne la première et la deuxième étape de la création du profil de connectivité insulaire. Le deuxième objectif serait ensuite de comparer les données structurelles obtenues avec celles de la présente étude afin de valider les résultats. Ainsi, nous obtiendrons une meilleure idée des réseaux auxquels pourrait appartenir l'insula et, de ce fait, comprendre davantage les implications neurologiques et cliniques s'y reliant.

Conclusion

En conclusion, l'insula est une structure intrigante tant par la richesse de son rôle intégratif que par les difficultés méthodologiques à surpasser afin de mieux la définir. Grâce au développement de nouvelles techniques d'investigation, l'exploration du rôle fonctionnelle et de la connectivité structurelle de l'insula sont plus accessibles. Comme le démontre l'étude dans ce mémoire, le profil de connectivité de l'insula commence à se clarifier. Bien qu'il reste encore un travail considérable de recherche à faire sur le rôle exact de l'insula dans les fonctions auxquelles elle est reliée, il est réaliste d'espérer que les récentes avancées permettront d'élucider la connectivité ainsi que le rôle de l'insula, considérée comme mystérieuse jusqu'à récemment.

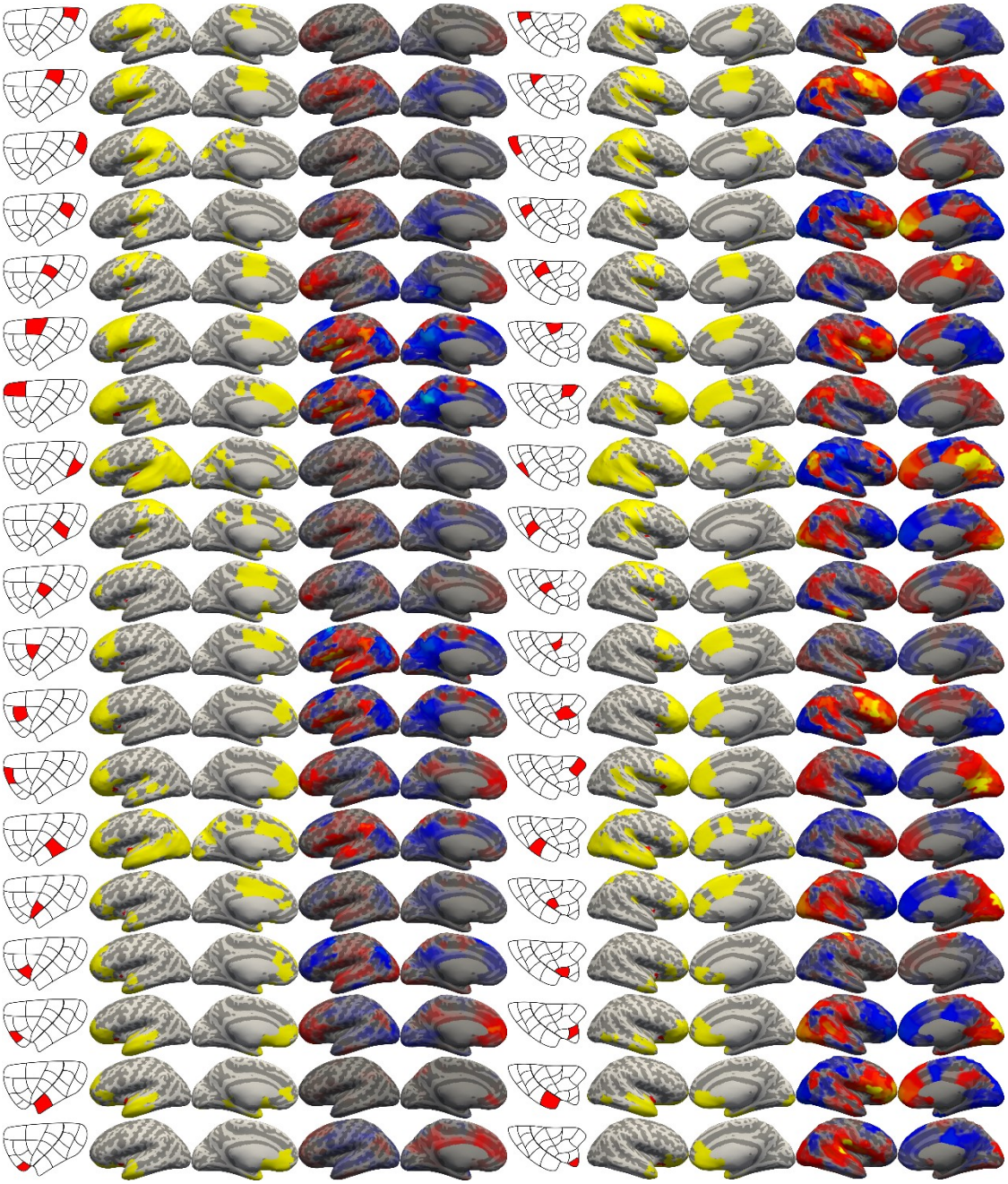

Figure 2. Résultats préliminaires comparant la connectivité structurelle (jaune) à la connectivité fonctionnelle (IRMfer) (rouge et bleu). Gauche = hémisphère gauche ; Droite = hémisphère droit.

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ANNEXES

ANNEXE 1

Chapter 2: The connectivity of the human insular cortex: a review

Published by:

Uddin LQ, editors. *Insula: Neuroanatomy, Functions and Clinical Disorders*. ed. New York: Nova Scien. 2014. p. 31–66

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Abstract

Most of the brain's cognitive functions are based on the coordinated interactions of large numbers of neurons that are distributed across different specialized brain areas. These brain areas are said to be organized like a 'small-world' network with abundant local connections to minimize wiring and energy cost but also relatively sparse long-range connections so that signals travel quickly from one brain area to another. This way, information processing is segregated to local structures but the processing is also integrated between distant structures. Structural networks form the backbone of neural connectivity, while functional networks make dynamic use of this backbone and transiently unite disparate brain regions. The insula, the fifth lobe of the brain, is a complex structure located in the depth of the Sylvian fissure and covered by the frontal, parietal and temporal opercula. Cumulative work over years has suggested that the insula is involved in several processes such as taste, hearing, olfaction, touch, pain, vestibular processing, interoceptive awareness of body states, neglect, empathy, disgust, craving, language, etc. It is likely that a large network of connections allows it to participate in these numerous functions. In the first part of this work, we will review information derived from tract tracing studies in nonhuman primates. Unfortunately, the majority of the human insula has no equivalent in the monkey as the brain has undergone a gradual increase in size and in the complexity of its organization in the course of primate and hominid evolution. Post-mortem studies in humans are hampered by the inability to use axonally transported tracers. Fortunately, advances in structural and functional neuroimaging techniques over the last decade have allowed a better glimpse of the connectivity of human insula. In the second part of this review, we will summarize these

observations derived from task-related functional MRI, resting-state functional MRI, tractography and intracerebral electroencephalography, recognizing that each of these methods have its distinct advantages and limitations.

Introduction

The insula is a pyramid-shaped structure enclosed in the depth of the Sylvian fissure. Its tip, the apex, is located in the antero-inferior portion and represents the most superficial part of the insula. It is divided by the central insular sulcus into an anterior portion made out of three short gyri (anterior, middle and posterior) and a posterior portion made of two long gyri (anterior and posterior) (Figure 1) (Augustine, 1996; Flynn, 1999; Türe, Yaşargil, Al-Mefty, & Yaşargil, 1999). These insular gyri form a fan-like pattern and converge anteriorly and inferiorly towards the vascular entrance of this region, the limen insulae containing the uncinate fasciculus in its underlying white matter. Up to 2 short transverse gyri are located at the orbito-frontal junction (Türe et al., 1999). Located directly under the insular cortex are in order: the extreme capsule, the claustrum, the external capsule (harbouring the arcuate fasciculus), the lenticular nucleus and internal capsule.

The insular lobe is considered the fifth lobe of the brain, the fourth region in Brodmann's cortical map including areas 13 through 16 (Brodmann, 1909; Stephani, Fernandez-Baca Vaca, Maciunas, Koubeissi, & Lüders, 2011). Histological investigations have shown that the architectonic division of the insular cortex does not necessarily follow its sulco-gyral division. Rather, based on the organization, shape, number and type of neurons, the insula is divided into three architectonic zones, arranged in a centrifugal manner: a) the phylogenetically oldest and least differentiated agranular zone (Ia; agranular allocortex) located rostroventrally at the limen insulae; b) the better differentiated granular zone (Ig; granular isocortex or neocortex) positioned caudodorsally, covering the dorsal posterior insula and in between, c) the dysgranular transitional (or intermediate) zone spanning from the anterior to the posterior

insula (M. M. Mesulam & Mufson, 1985). The terms granular and agranular refer to the presence or absence of an internal granular layer (IV), respectively. Within the agranular zone, two architectonically distinct zones were subsequently identified, one of which possessed a *lamina dissecans* and the other did not (Preuss & Goldman-rakic, 1989; Augustine, 1996). The transitional zone is termed dysgranular because granule cells are scarce in layer IV and do not display complete laminar differentiation. A special feature of the anterior insular cortex is that its fifth layer contains, in addition to pyramidal neurons, numerous large spindle-shaped cells (called von Economo neurons), observed also in the anterior cingulate cortex (Economo, 1926; Nieuwenhuys, 2012). The retroinsular area, located posteriorly to the insula at the junction of the parietal and temporal opercula, has a cytoarchitecture that is intermediate between that of the granular zone and the temporoparietal cortex (Augustine, 1996; E. G. Jones & Burton, 1976).

Insular connectivity in non-human primates

With the discovery in the mid-twentieth century of tract-tracing methods such as tritiated amino acids (TAA) and horseradish peroxidase (HRP) allowing axonal tracing of neuronal pathways using anterograde and retrograde transport (Oztas, 2003), the study of the insular cortex connectivity became more prominent in non-human primates. Retrograde axonal transport allows the identification of the cells of origin of afferent nerve fibers to a particular target zone whereas anterograde axonal transport enables the projection target of individual or groups of cells to be charted within the central nervous system (CNS) (Köbbert et al., 2000). In this section, we will focus mainly on studies of the macaque insula because of their sheer

number in the literature and because the monkey's insular architecture is the closest to the human.

The cumulative work from the past 30 years has shown that the insular cortex is connected with the cerebral cortex (frontal, parietal and temporal), the basal ganglia, some limbic and paralimbic structures such as the amygdala and the thalamus. Below, we will summarize the efferent, afferent and reciprocal connectivity of the insular cortex with these regions and their subregions but interested readers are invited to read the seminal work of Mesulam (1982a, 1982b) and Mufson & Mesulam (1982) and the more recent excellent reviews by Augustine (1996) and Nieuwenhuys (2012).

Frontal lobe

The insular cortex sends widespread efferent projections to the frontal lobe: Area 6 (homologous to the human agranular frontal area 6 composed of the premotor cortex and supplementary motor area) including Area F3 (supplementary motor area-proper) and Area F6 (presupplementary motor area), the prefrontal cortex (including the inferior frontal gyrus, the frontal operculum, the orbital cortex) and the cingulate gyrus (Areas 23, 24) (E. Mufson & Mesulam, 1982). Work from Mesulam and others have sorted these connections by architectonic sectors. The insular agranular zone sends projections to the anterior cingulate areas 24a and 24b while the granular zone sends projections to the posterior cingulate area 23 (M. Mesulam & Mufson, 1982a; B. a Vogt & Pandya, 1987; B. A. Vogt, Pandya, Rosene, & Paniiya, 1987). The insular dysgranular zone sends projections to the frontal area F6 (presupplementary motor area), the frontal operculum, the ventral granular frontal cortex and the orbital cortex. The insular granular zone has efferent projections to the ventral granular

frontal cortex as well and the frontal area F3 (supplementary motor area proper). Frontal afferent connections to the insula take origin in the prefrontal cortex, orbitofrontal cortex (including the olfactory tubercle and olfactory bulb) and frontal operculum.

Parietal lobe

The insular cortex shares reciprocal connections with the primary and secondary somatosensory cortices, including the parietal operculum, area 5 and the retroinsular area (Augustine, 1996; M. Mesulam & Mufson, 1982a). Architectonically, it is known that the second somatosensory cortex reciprocally connects with the insular dysgranular and granular zones while the retroinsular area reciprocally connects with the insular granular zone.

Temporal lobe

The insular cortex has efferent projections to the temporal pole/temporopolar cortex, the superior temporal sulcus and supratemporal plane. Afferents from the temporal lobe reaching the insular cortex come from the auditory cortex (primary auditory cortex, auditory association cortex and postauditory cortex), temporal operculum, superior temporal cortex/superior temporal sulcus and the temporal pole. Sorted architectonically, the agranular insular zone has efferent projections to the temporal pole dysgranular zone, the anterior superior temporal sulcus and primary auditory cortex (Augustine, 1996; E. Mufson & Mesulam, 1982). The anterior insular dysgranular zone has efferent projections to the temporal pole dysgranular zone, the anterior superior temporal sulcus, the prepiriform portion of the olfactory cortex, the prorhinal and entorhinal cortices. The posterior insular dysgranular zone

connects to the anterior superior temporal sulcus (Augustine, 1996; E. Mufson & Mesulam, 1982). Presumably, the insular granular zone has efferent projections to the temporopolar cortex. The dysgranular insular zone receives afferent projections from the superior temporal sulcus and the temporopolar cortex. The insular granular zone receives afferent connections from the temporopolar cortex as well.

More medially, the insular cortex has reciprocal connections with the amygdala. The dysgranular insular zone sends projections to the lateral nucleus and to the cortical and medial amygdaloid area. The insular granular zone sends projections to the lateral basal nucleus of the amygdala and receives projections from the lateral nucleus of the basolateral part of the amygdala. Other medial temporal structures that have connections to the insular cortex include the periamygdaloid cortex, anterior hippocampus, entorhinal/prorhinal/perirhinal cortices, temporal piriform cortex and endopiriform nucleus, and parahippocampal gyrus. Architectonically, there are known projections from the insular agranular zone to the periamygdaloid, prorhinal and entorhinal cortices and from the insular dysgranular zone to the perirhinal cortex. There are also projections from the entorhinal cortex to the agranular insular zone and fewer ones to the insular dysgranular and granular zones as well.

Subcortical structures

Studies have revealed that the insular cortex also has projections to (and receives projections from) several thalamic nuclei (especially the dorsal thalamus), the basal nuclei (notably the lentiform nucleus, tail of the caudate, putamen and claustrum) and the hypothalamus. There are also connections from the insular cortex that enter the white matter

towards the internal capsule, external capsule, anterior commissure and the corpus callosum (Augustine, 1996; Berke, 1960; Krieg, 1965).

Limitations

Tract-tracing studies have some limitations. For one, the depth of the insular cortex makes it difficult to access it without damaging its surroundings. Tracer injections vary with survival time, fixation procedure and histochemical sensitivity affecting the efficiency of the uptake and the estimates of neural projections. In addition, some of the projections mentioned above might have been a reflection of the uptake of injected tracers by nearby structures such as the claustrum, extreme capsule or even the putamen (Barbas & Mesulam, 1981; Mesulam et al. 1977; E. J. Mufson & Mesulam, 1984). Furthermore, the data is collected purely by visual inspection using subjective nonstandardized criteria and small sample sizes. Finally, although monkeys have complex brains and it is assumed that there is basic comparability between the insular cortex of humans and nonhuman primates, care must be taken when extrapolating to humans as the human insula is 30% larger and more complex (Semendeferi & Damasio, 2000). For example, von Economo neurons have not been found in the macaque (Craig, 2009). To study the human brain, autopsied human brain specimens have been used numerous times in attempts at unravelling cortical connectivity with methods that have ranged from hand dissection to tracing the degeneration caused by focal brain damage and the local diffusion of dyes (Marsel Mesulam, 2005). However, these are severely limited as the inability to control variables such as post-lesion survival, agonal state, and fixation parameters, and the obvious

inability to use axonally transported tracers greatly affect the quality of the data generated by these approaches.

Insular connectivity in humans

Advances in structural and functional neuroimaging techniques over the last decade have allowed a better insight of the connectivity of human insular cortex. The methods to investigate the connectivity of the human insula are divided into structural and functional techniques, each with its distinct advantages and limitations. Structural connectivity techniques are designed to identify fibers connecting disparate brain regions. Functional connectivity analytical techniques are designed to infer connections between regions of interest of a system by identifying common patterns between spatially separated signal fluctuations (whether they are BOLD signals, EEG or magnetic fields) of the components in the system. In this section, we will summarize observations from both structural (tractography) and functional (resting-state functional MRI, functional MRI, electroencephalography) techniques, being cognizant that with each of these methods there are advantages and disadvantages.

Functional MRI

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging method that uses blood-oxygen-level-dependent (BOLD) changes (i.e. hemodynamic and oxygen consumption) to spatially map brain functions associated with task-specific activations

(Logothetis, 2008). This technique is mostly used to confirm functional activations of brain regions based on prior knowledge using a cross-correlation analysis.

Whether the insula was the center of interest or a collateral discovery, it has been widely reported in fMRI protocols, most likely because of its multimodal and integrative role (See special issue of Brain Structure and Function on the insula, 2010). Paradigms pertaining to emotion, empathy, olfaction, gustation, interoception, pain, somatosensation, motion, attention, language, speech, working memory and memory are frequently reported to activate the insular cortex (Mustschler et al., 2009; Wager and Barrett, 2004; Kurth et al., 2010). For example, in fMRI and PET studies, empathy commonly activates a network comprising the dorsal anterior cingulate cortex, anterior mid-cingulate cortex, the supplementary motor area and bilateral anterior insula (Fan et al., 2011). Emotional tasks activate various brain regions in different aspects of emotions, commonly the medial prefrontal cortex, the amygdala, the anterior cingulate cortex and the insular cortex (Phan et al., 2002). The extended olfactory network encompasses the primary olfactory cortex, the orbitofrontal cortex, the insula, the hypothalamus, the amygdala, the perirhinal cortex, the hippocampus, the striatum, the dorsolateral prefrontal cortex, the rostral prefrontal□anterior cingulate, and the parietal-occipital junction (Karunanavaka et al., 2013; Small and Prescott, 2005). The four main functional linked regions associated with pain processing include the primary and secondary somatosensory cortex, the anterior cingulate cortex and the insula (Fomberstein et al., 2013; Budell et al., 2010). There is a vast literature of fMRI studies reporting insular activations whose review is obviously beyond the scope of this chapter. Nonetheless, these task-fMRI experiments have generally found functional co-activations in areas that are reported to be

structurally linked to the insular cortex in macaque tracing studies. Because different aspects of the function may be tested during individual experiments, additional areas may be activated (e.g. the visual cortex with emotional induction by visual stimuli) and thus detailed analysis of each article is generally necessary to better interpret areas activated by the paradigm used.

Over the last decade, a few meta-analyses on insular activations have been performed (Mutschler et al., 2009; Wager and Barrett, 2004; Kurth et al., 2010), with the most recent by Kurth et al. In the latter, the authors performed activation-likelihood-estimation meta-analyses of 1.768 functional neuroimaging experiments with insular activations (811 papers; 11,796 subjects). They observed that sensorimotor paradigms activated mainly the mid-posterior insula, social-emotional tasks the anterior-ventral insula, olfacto-gustatory stimuli the central insula, and cognitive tasks the anterior-dorsal region preferentially. Aside from basic somatosensory and motor processes, all tested functions overlapped on the anterior-dorsal insula, supporting the hypothesis that it may have an important integrative role between different functional systems.

Limitations

Several shortcomings exist when using fMRI. It essentially measures a substitute signal subject to spatiotemporal restrictions based on two main constraints (Logothetis, 2008). Firstly, the physics constraint, for instance poor spatial resolution compared to anatomical images (3 to 5 mm resolution for fMRI, while cortical thickness varies between 1 to 4mm (Fischl, 2000) leading to strong partial volume effect), relaxation times and thermal noise (for a review, see Constable, 2012) . Secondly, the physiological factors such as the heartbeat and

respiration or subject movements (Constable, 2012). The low temporal resolution (usually around 1 volume every 3 seconds for recent fMRI protocols) make it difficult to differentiate activation patterns resulting from proximate stimuli. Different approaches such as block designs, independent analysis, arterial spin labeling, and event-related, which will not be discussed further, exist and differ in their methods and results. These mostly rely on linearity between neural activity and hemodynamic responses, whereas brain processes are highly nonlinear (Detre & Wang, 2002; Li, Guo, Nie, Li, & Liu, 2009; Logothetis, 2008). Similarly, maps obtained by fMRI are static representations of the dynamic activity and the time-frame does not match (R. Menon & Kim, 1999). In line with the approaches, study designs do not take into consideration the circuitry and the functional organization of the brain, while the parameters, such as the statistical threshold, are chosen arbitrary (Constable, 2012; Logothetis, 2008). Therefore, task-related fMRI experiments have to be interpreted with care. Finally, tasks have to be carefully designed and analysis can be particularly challenging when considering processes that are conceptually difficult or that do not have an easily definable task associated with them. There will always be some ambiguity in categorizing the cognitive processes under study. For example, pain and interoception are not solely sensory processes, but also have an important emotional and empathy component. The same is true in some capacity for nearly all categories (Kurth et al., 2010).

Resting-state fMRI

Resting-state fMRI (rsfMRI) is a technique used to study functional systems of the brain's neural activity while at rest. More precisely, it reveals the synchronous activations between

different regions that are spatially distinct in the absence of a task (Lee, 2012; Thomason et al., 2011; Zang & Zhao, 2012). Simultaneous functional activation of the insular cortex and other cortical and subcortical regions will be briefly reviewed in this section. Since there is no consensus on standard methodology to analyze rsfMRI data, the different techniques will not be reviewed in this chapter. Most of the studies use FMRIB's software library (FSL, Analysis Group, FMRIB, Oxford, UK), Matlab's Statistical Parametric Mapping library (SPM, Wellcome Trust Centre for Neuroimaging, UCL, London, UK), or home-made tools, but the steps (i.e. preprocessing) differ widely.

The majority of rsfMRI studies on the functional connectivity of the insular cortex have described a division following an anterior and posterior part. The anterior insula has been mostly activated with the frontal, parietal and temporal cortices, the cingulate gyrus, the basal ganglia, the thalamus and the amygdala. As for the posterior insula, it has mostly been activated with the frontal, parietal and temporal opercula, the dorsal anterior cingulate cortex and posterior cingulate cortex, the thalamus, the precentral and postcentral gyri, and the occipital lobe (See Table 1).

Insert Table 1 here

Some isolated regions have been reported only from single studies and are excluded from Table 1. Among these regions are the cerebellum, pons and basal ganglia that were activated with the right insular cortex, while the putamen was activated with the anterior, middle and posterior insula (Cauda et al., 2011).

Limitations

One of the major limitations of rsfMRI is the influence of physiological noise such as the heartbeat, respiration and signal fluctuation (Birn, 2012). A second major limitation is the lack of standard data processing with rsfMRI images. There are several methods available, such as seed-based functional connectivity (Biswal, 1995), independent component analysis (Kiviniemi, Kantola, Jauhiainen, Hyvärinen, & Tervonen, 2003), clustering, pattern classification (Norman, Polyn, Detre, & Haxby, 2006), graph theory and local methods, each with advantages and disadvantages (for review, see Margulies et al., 2010). Depending on the choice of the technique, false positives or false negatives are increased. Furthermore, some methods require a priori knowledge while no information is known about spatial and temporal resolution of rsfMRI (Li, 2009).

Tractography

Diffusion-weighted imaging (DWI) is an in-vivo MRI technique that uses magnetic field gradients, sent in multiple different directions following a sphere, to obtain information about the diffusivity of water molecules of the brain tissue. Fiber tracts constrain water molecules to follow their direction; if the gradients and the water molecules have the same direction, a signal decrease will occur. Diffusion-tensor imaging (DTI) uses this information to provide the orientation of water molecules in each voxel and its diffusion anisotropy, allowing the estimation of axonal organization of the brain. DTI only estimates the principal direction and cannot differentiate between a lack of diffusivity and equal diffusivity in all directions preventing the analysis of crossing fibers, which constitute most of the brain. High angular

resolution diffusion imaging (HARDI) requires more directions (strict minimum 15, but to correctly infer multiple directions, an average of 40 is usually needed) compared to the minimum of six required by DTI. The latter estimates the probability of connectivity of two regions only on one fiber population per voxel, while HARDI tracks white matter fibers on multiple fiber populations per voxel reducing false negative connections between regions of the brain. Fiber tracking can be induced with these methods and represents the only non-invasively technique to study in-vivo white matter tracts in the human brain (Jbabdi & Johansen-Berg, 2011; Le Bihan, 2003; Mori & van Zijl, 2002; Mori & Zhang, 2006; for a review, see Tournier, 2012; Tuch et al., 2002).

The principle behind fiber tracking consists of creating regions of interests (ROIs) with seeds as a starting point where an estimation of the fiber population will follow the principal direction step by step. The pathway is traced based on the closest fiber orientation to the one previously chosen. In order to avoid false positives, constraints will usually be set on the maximum curvature, total length (to avoid loops), and binary or probabilistic masks of the white matter. Unfortunately, no standard criterion exists for these restrictions. Therefore, different results can be reported depending on the values that have been determined. Numerous software solutions, methods and pipelines exist with no real standard in analysis of structural connectivity, making comparisons between existing research challenging. In this chapter we will mainly discuss the findings on insular connectivity with only a brief description of the method intended for specialist readers. For more information about the methodology, readers are invited to consult the cited research papers.

To our knowledge, only three studies have been published on the connectivity of the human insular cortex (Cerliani & Thomas, 2012; Cloutman, Binney, & Drakesmith, 2012; Jakab, Molnár, Bogner, Béres, & Berényi, 2012) and a single study on its development between the ages of 12 and 30 (Dennis et al., 2013). The first study by Cloutman et al. (2012), is based on twenty subjects using a 3Tesla MRI scan and the probabilistic index of connectivity (PICo) method (Parker, Haroon, & Wheeler-Kingshott, 2003) to sample the orientation of probability density functions (PDFs) (J.-D. Tournier et al., 2008), generated using the constrained spherical deconvolution method intended to increase the angular resolution (Descoteaux, Deriche, Knösche, & Anwander, 2009). The objective was to map the structural connectivity of insular subregions. Twenty thousand streamlines were drawn from each voxel with a step size set to 0.50mm and a stopping curvature value of a maximum of 180º or a maximum length of 500mm. DARTEL toolbox (Ashburner, 2007) under SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) was used for normalization. Fibre pathways were determined using brain region masks from the Automated Anatomical Labeling (AAL) atlas (WFU Pick Atlas - Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). Seven regions of interest (ROIs) were created to explore any topographic or cytoarchitectonic differences in the insular connectivity between anterior-posterior and dorsal-ventral regions. Using probabilistic tractography, the authors reported similar connectivity for both hemispheres. The connection patterns revealed three insular subdivisions, an anterior, a posterior and an intermediate region. The results reported from the anterior region showed connectivity with orbitofrontal, inferior frontal (triangular and opercular) regions, anterior temporal areas and posterior middle temporal gyrus in an exclusively ventral pathway

involving fibre tracts such as the uncinate fasciculus, extreme capsule and the inferior fronto-occipital fasciculus. The posterior region was predominantly connected with posterior superior and middle temporal areas, the anterior superior or temporal gyrus, and the rolandic operculum via both dorsal and ventral pathway involving the extreme capsule and the arcuate fasciculus. The intermediate region demonstrated a graduated pattern of hybrid connectivity to frontal and temporal regions, rolandic operculum, the postcentral gyrus, and the supramarginal gyrus via a predominantly dorsal pathway. These findings are in agreement with human rsfMRI functional connectivity data (Cauda et al., 2011; Deen, Pitskel, & Pelphrey, 2011) and nonhuman primates tract-tracing studies summarized above (M. Mesulam & Mufson, 1982a, 1982b; E. Mufson & Mesulam, 1982).

The second study, published by Cerliani et al. (2012) is based on ten subjects using a 3Tesla MRI scan and FMRIB's diffusion toolbox to perform probabilistic tractography. For each single voxel, a fiber population has been generated from 5000 tracks resulting in a connectivity matrix comprising reached voxels and the number of fibers crossing each voxel. Connectivity of reached voxels were increased by the length of fiber tracts to avoid connectivity drops due to long-range fasciculi (Beckmann, Johansen-Berg, & Rushworth, 2009; Eickhoff et al., 2010; Tomassini et al., 2007). ROIs were created following the method by Naidich et al. (2004) in order to identify anatomical landmarks, and the terminology mediated by Ture et al. (1999). Only voxels with 50 or more tractography samples and present in at least half of the participants were analyzed. The authors found a rostrocaudal pattern of connectivity. The anterior insula projected to the orbitofrontal cortex, the inferior frontal

gyrus, the dorsal part of the temporal pole, and the centromedial nucleus and laterobasal complex of the amygdala. The dorsal caudal insula projected to the parietal lobe, posterior regions of the temporal lobe, the inferior frontal gyrus, the left dorsolateral prefrontal cortex and extrastriate regions of the occipital cortex medially and laterally. The middle insular regions had a mixed connectivity pattern between the anterior and posterior insula and were mostly connected to the lateral and medial premotor cortex, temporal and parietal lobes, inferior frontal gyrus and orbitofrontal cortex. Moreover, connectivity asymmetries were reported in the right hemisphere with BA44 (inferior frontal gyrus) and the superior parietal lobe, and in the left hemisphere with limbic regions and BA6 (premotor cortex and supplementary motor area). These findings essentially corroborate the findings by Cloutman et al. (2012).

The third study was published by Jakab et al. (2012) and is based on 40 subjects using a 1.5Tesla MRI scan. The goal was to examine the organization of the human insular cortex based on the similarities of its remote projections. The FMRIB diffusion toolbox was used to run a probabilistic diffusion tractography. Diffusion images were normalized on the FSL Fractional Anisotropy (FA) template in the standard Montreal Neurological Institute (MNI152) space using non-linear registration, The Harvard-Oxford atlas in the MNI152 space were used to extract insular regions, and for each subject, ROIs were manually refined using its native T1. A k-mean clustering algorithm on the connectivity matrix subdivided the insula into 2 distinct regions: an anterior and a posterior one, in both hemispheres. The first one was reported to have projections with the medial dorsal thalamus, the temporal and occipital lobes,

the orbitofrontal and inferior frontal gyrus. As for the second one, connections with the parietal and frontal lobes, and the ventrolateral thalamus were reported. Similarly to the study by Cerliani et al. (2012), connections in the occipital lobe were noted.

The fourth and last study published by (Dennis et al., 2013) is mainly based on the insular cortex' structural connectivity strength changes along the age span and does not focus on its connections with cortical and subcortical regions. Therefore, their results will not be reviewed in this chapter. However, it is noteworthy that the regions reported as being connected with the insula, such as the frontal, parietal and temporal cortices, the temporal pole, the supramarginal, postcentral, precentral, temporal, orbitofrontal and parietal gyri, are similar to the previous studies reviewed earlier.

Insert Table 2 here

Limitations

Although tractography is the most advanced in-vivo method available to study white matter tracts in humans and the closest to tract-tracing in animals, it too has some limitations. All DWI-tractography based techniques have low spatial resolution, lack histological validation and lack empirically supported gold standard criterion for determining the threshold value and the number of streamlines, and the inability to discriminate between afferent and efferent projections (Cerliani & Thomas, 2012; Cloutman et al., 2012; Dell'Acqua & Catani, 2012). DTI-based probabilistic tractography estimates the probability that a pathway exists between two regions and is restricted to one fiber direction per voxel while multiple fiber

directions exist making the crossing-fiber problem the major limitation of this technique (for a review, see Farquharson et al., 2013; Frank, 2002; Jakab et al., 2012; Jbabdi & Johansen-Berg, 2011; for a review, see J. Tournier, Mori, & Leemans, 2011; J.-D. Tournier, Calamante, & Connelly, 2007). Therefore the connection cannot be established with certainty, making it vulnerable to type I errors in the region close to the seed, and type II errors in more distant regions (Cloutman et al., 2012; Jakab et al., 2012; D. K. Jones, 2008; Morris, Embleton, & Parker, 2008). Small fibre tracts might be lost when crossing larger tracts like the longitudinal fasciculus and the corona radiata (Dougherty, Ben-Shachar, Bammer, Brewer, & Wandell, 2005). Long pathways are more difficult to identify as the longer the pathway, the higher the probability of connectivity decrease and streamline dispersion (Cloutman et al., 2012; Morris et al., 2008). This may explain why no tractography study has yet found structural connectivity between the insula and the cingulate cortex in humans despite functional task-related and resting-state functional imaging findings and tract-tracing evidence in macaques as mentioned above. New algorithms and approaches are continuously being developed such as diffusion spectrum imaging (DSI), which can help reduce false negative results and more optimally detect crossing-fibers within white-matter in cortical and subcortical structures (Wedeen, Wang, & Schmahmann, 2008).

The studies reviewed above were based on a relatively low number of subjects and ROIs based on a sulco-gyral division. Unfortunately, macroscopic sulco-gyral features are not reliable landmarks of cytoarchitectonic borders (Amunts et al., 1999; Fischl et al., 2008). Furthermore, the proximity of other white matter bundles around the insular cortex, such as

the extreme capsule (Makris & Pandya, 2009), the external capsule/corona radiata, the uncinate fasciculus, the arcuate fasciculus (Nieuwenhuys, Voogd, & Van Hujzen, 1988) and the inferior fronto-occipital fasciculus can affect tractography results by showing for example, connections with the occipital lobe. In this perspective, no studies in humans or animals have shown structural connections between the occipital lobe and the insular cortex though, some have reported direct connections between the claustrum and parieto-occipital regions (Crick & Koch, 2005; E. Mufson & Mesulam, 1982; Shipp et al., 1998; Tanné-Gariépy, Rouiller, & Boussaoud, 2002) in animals, while in humans, connections between the claustrum and the occipital lobe were found via the inferior fronto-occipital fasciculus (Catani et al. (2002) (Schmahmann & Pandya, 2007; Schmahmann et al., 2007, from Cerliani & Thomas, 2012). Further investigation is necessary as functional connectivity have been recently found between the two regions (Cauda et al., 2011; V. Menon & Uddin, 2010; Roy et al., 2009).

Preliminary results

Preliminary results from an ongoing tractography study of the insular cortex by our group will be presented in this section. Probabilistic fibre-tracking was performed using probabilistic tractography (Figures 2) from the MRtrix package (J-D Tournier, Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/) (J. Tournier, 2012) on 17 out of a total of 50 subjects using gyri parcellation based on FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) (Dale, Fischl, & Sereno, 1999a, 1999b; Desikan et al., 2006). The structures identified in the frontal, temporal and parietal lobes connected to the insular cortex were similar to those in the above studies. In addition, by using methods to

detect crossing-fibres and pass by the corona radiata, we show structural connectivity to the cingulate cortex (as suggested by rsfMRI data in humans and tract-tracing studies in macaques). In agreement with the earlier structural studies summarized above (Cerliani & Thomas, 2012; Cloutman et al., 2012), a rostrocaudal trajectory of connectivity was confirmed by quantitative statistical analysis after manually separating the insular cortex in an anterior and posterior portion. Interhemispheric differences were also found, the right one being less connected globally than the left.

The final analysis on the data obtained from 50 healthy subjects using small ROIs randomly distributed and up-to-date state of the art connectivity methods is ongoing.

-Insert figure 2 around here-

Intracranial EEG recordings

In some specialized epilepsy surgery units such as ours, direct exploration of the insula (among other regions) using intracranial electrodes is performed on a regular basis to delineate more precisely the epileptogenic zone when non-invasive techniques cannot. These recordings represent a unique opportunity to study the connectivity of the human insula. Epilepsy is a chronic condition characterized by recurrent seizures (or 'ictus') resulting from abnormal and excessive neuronal discharges. Temporal and frontal lobe seizures are the two most common types of focal seizures but insular seizures are more and more frequently recognized (D K Nguyen, Surbeck, Weil, Villemure, & Bouthillier, 2009; Dang Khoa Nguyen et al., 2009; Surbeck, Bouthillier, & Nguyen, 2010). The major course of treatment involves long-term

drug therapy to which approximately 30% of patients are unfortunately refractory. Brain surgery is recommended when medication fails and the seizures are confined to one area of the brain where tissue can be safely removed. To localize the epileptogenic zone, patients first undergo a non-invasive comprehensive presurgical evaluation that includes a cerebral magnetic resonance imaging, video-scalp electroencephalography (EEG) monitoring, magnetoencephalography and ictal single photon emission computed tomography. When these complementary non-invasive studies fail to adequately localize the epileptogenic zone, an invasive EEG study is required consisting of the implantation of intracranial electrodes through a craniotomy or burr holes under general anaesthesia in areas of suspected epileptogenicity (Spencer, 2009). Patients are then transferred to the epilepsy monitoring unit for continuous video-intracranial EEG monitoring, awaiting seizures. Once a sufficient number of seizures have been recorded, the patient is brought back to the operating room for the removal of electrodes and resection of the epileptogenic zone (if successfully identified by these recordings). These intracerebral recordings provide a window of opportunity to study the connectivity of the human brain. Work from the last few years (particularly from detailed analysis of data generated by intracranial EEG) suggests that network connectivity is at the center of epilepsy (Spencer et al., 2002). A more complex 'epileptic network' concept has emerged replacing the classical notion of a single epileptic focus. In the 'epileptic network', the synchronized activity of 'nodes' with increased excitability (or decreased inhibition) are involved in the generation of pathological 'interictal epileptic spikes' (brief asymptomatic paroxysmal EEG transients clearly distinguished from background seen in between seizures) and 'seizure onset fast oscillations' (sudden focal rhythmic activity with a characteristic

pattern of evolution in amplitude, frequency and spatial distribution lasting at least several seconds and associated with clinical manifestations) (M. Kramer & Cash, 2012; Lemieux, Daunizeau, & Walker, 2011). Vulnerability to seizure activity in any one part of the network is influenced by activity everywhere else in the network, and the network as a whole is responsible for epileptic discharges and seizures. The network structures are connected functionally and structurally and seizure activity can be entrained from any of its various parts. One (or more) node(s) would have a level of excitability so high that it (they) would autonomously generate seizure onset fast oscillations, driving or entraining through excitatory connections other distant nodes (acting as relays of those fast oscillations). Seizures can subsequently propagate in an extensive and variable pattern that might involve any region or neural structure with anatomic connections to the primary seizure network. Over the last few years, the epileptogenic networks of temporal lobe epilepsies have been described using such intracranial EEG recordings (Bartolomei, Wendling, Bellanger, Régis, & Chauvel, 2001).

At our institution, we have observed complex (but relatively reproducible) electrophysiological patterns often involving several spatially distinct structures of a broad network during interictal insular spikes, with insular seizures and during insular electrical stimulation. Examples of intracerebral EEG recording of insular spikes and seizure are given in Figures 4-5. Upon visual qualitative analysis, interictal spikes detected by depth electrode insular contacts □U1 (1-2)□ are also registered synchronously over the lateral orbitofrontal cortex □F1 (4)□, the inferior frontal gyrus □G1 (3)□ and more distantly the anterior medial frontal gyrus □I1 (3)□. The onset of seizures is characterized by the appearance of fast (20-30 Hz) activity dramatically differing from interictal background activity and involving several

distinct structures notably the orbitofrontal cortex, the inferior frontal gyrus, the medial frontal gyrus and the temporal lobe. These structures are in line with findings from tract tracing studies in macaques and rsfMRI/tractography studies in humans mentioned earlier. Epileptic patients participating in intracranial EEG study will also frequently undergo one or several sessions of direct electrical stimulation to delineate eloquent cortices, i.e. crucial functional regions to be spared by surgery. Direct electrical stimulation data can also be used to study the functional connectivity of the brain. The primary targets of electrical stimulation are axons (in particular the initial segment) rather than cell bodies and each stimulated area is in fact an input gate into a large-scale network rather than an isolated discrete functional site. Brain regions showing specific responses to direct stimulation of a brain region are functionally connected to it (David, Bastin, Chabardès, Minotti, & Kahane, 2010; Lacruz, García Seoane, Valentin, Selway, & Alarcón, 2007). Responses to DES usually consist of a sharp deflection followed by a slow wave. Another type of response is 'after-discharges', which are essentially epileptic spikes triggered by electrical stimulation. Figure 6 shows an example of such responses triggered by insular cortical stimulation in a patient from our institution. Evoked after-discharges, similar to spontaneous discharges, are noted not only in the anterior insula but also in the lateral orbitofrontal cortex, the inferior frontal gyrus and the anterior cingulate gyrus, again congruent with macaque tracing studies and human rsfMRI studies.

During the past decades, considerable effort has been devoted to the development of signal analysis techniques aimed at characterizing the functional connectivity among spatially distributed regions over interictal (outside seizures) or ictal (during seizures) periods from EEG data. Most of these methods rely on the measurement of statistical couplings among

signals recorded from distinct brain sites. With these technical advances, it is likely that over the next few years, a more robust map of the complex connectivity of the insula and its subregions can be obtained (Cui, Xu, Bressler, Ding, & Liang, 2008; M. Kramer et al., 2010; M. Kramer, Eden, Cash, & Kolaczyk, 2009; Seth, 2010; Wendling, Chauvel, Biraben, & Bartolomei, 2010). In the literature, functional connectivity studies using cortical electrical stimulation have dwelled into connections of the temporal and frontal lobes but only one study has looked at the insula to our knowledge. Almashaikhi et al. (2013) performed intracerebral electrical stimulation in 10 patients with refractory epilepsy investigated with depth electrodes (38 insular contacts). All insular gyri were found to be interconnected, except the anterior and posterior short gyri. Most connections were reciprocal, showing no clear anterior to posterior directionality. No connection was observed between the right and left insula. As interesting as these findings are their interpretation is hindered by the number of patients, electrodes and the regions investigated. The reported connectivity is limited to two or four patients out of a total of ten. Furthermore, very few regions are compared whether it be interregional (anterior vs. posterior), interhemispheric (right vs. left) or interpatient.

Limitations

The design of intracranial EEG studies varies from patient to patient. For each patient, the number and types of electrodes and the structures that need to be sampled depend on results from the non-invasive presurgical investigation. As a result, connectivity analyses are limited to the structures that are sampled. Another limitation lies in observing insular connectivity in pathological brains, which may be different from normal subjects, as structural changes may have occurred from repeated seizures. This limitation can be partly addressed by

separately analysing results obtained from direct insular electrical stimulation in patients whose seizures were found in the end to originate from a structure other than the insula. Furthermore, connectivity may also be addressed by analyzing baseline fluctuations rather than pathological fluctuations such as spikes and seizures.

Conclusion

In summary, multimodal evaluation of insular cortex connectivity has revealed relatively congruent gross findings. Linked structures commonly identified include the thalamus, the somatosensory cortex, the amygdala, the temporal pole, the superior temporal gyrus, the auditory cortex, the inferior frontal gyrus, the orbitofrontal cortex, and the prefrontal cortex. The insula is most likely connected to the cingulate cortex and supplementary motor area□premotor cortex although tractography data in humans is lacking. Some regions still lack consensus such as the putamen and the occipital lobe. Since tract-tracing studies are difficult in humans, exploiting the wide array of techniques described above in a large number of patients and with the benefit of further methodological improvements will hopefully allow us to obtain a more refined map of insular cortex connectivity.

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Authors	Insula	FC	IFG	OFC	PrC	PoC	SMC	SMA	SMG	ACC	MCC	PCC	PC	FO	PO	TO	TC	OC	TH
Van Den Heuvel et al. (2009)	Bilateral									X	X	X					X		
N= 26																			
3T																			
Taylor et al. (2009)	Anterior									X	X								
N= 19																			
3T	Posterior										X								
Deen et al. (2011)	Anterior		X	X	X			X	X	X			X	X	X	X	X	X	X
N = 30																			
3T	Posterior		X		X	X		X		X				X	X	X	X		X
Cauda et al. (2011)	Anterior		X						X	X			X				X		X
N = 17																			
1.5T	Anterior[1]	X[1]							X[1]	X[r]									X[1]
	Anterior[2]							X											
		X[2]																	
	Posterior						X	X			X	X	X				X	X	
	Posterior[2]				X	X											X	X	X[2]
Cauda et al. (2012)	Anterior	X								X	X	X	X						
Meta-analysis																			
	Posterior						X					X					X		

Table 1. FC= Frontal cortex; IFG= Inferior frontal gyrus; OFC= Orbitofrontal cortex; PrC= Precentral gyrus; PoC= Postcentral gyrus; SMC= Somatosensory cortex; SMA= Supplementary motor area; SMG= Supramarginal gyrus; ACC= Anterior cingulate cortex; MCC= Middle cingulate cortex; PCC= Posterior cingulate cortex; PC= Parietal cortex; FOp= Frontal opercula; POp= Parietal opercula; TOp= Temporal opercula; TC= Temporal cortex; OC= Occipital cortex; TH= Thalamus. 1= Right hemisphere; 2= Left hemisphere; r= rostral.

Cortical and subcortical regions	AIC	MIC	PIC
Superior frontal gyrus		1, 2	3
Inferior frontal gyrus		1, 2	2, 3
Orbitofrontal cortex	1, 2, 3	2	
Precentral gyrus		1	1
Postcentral gyrus		1	1
Supramarginal gyrus		1	
Parietal cortex		2	2, 3
Anterior temporal gyrus	1, 2, 3	2	1
Posterior temporal gyrus	1, 3	2	1, 2
Temporal pole	2		
Occipital cortex	3		3
Thalamus	3		3
Amygdala	2		
Putamen			1

Table 2. AIC = anterior insular cortex; **MIC** = middle or intermediate insular cortex; **PIC** = posterior insular cortex; **1** = Cloutman et al. (2012); **2** = Cerliani et al. (2012); **3** = Jakab et al. (2012). Due to the diversity of the nomenclature used in the literature and for simplicity purposes, the names of the regions were regrouped into more inclusive ones.

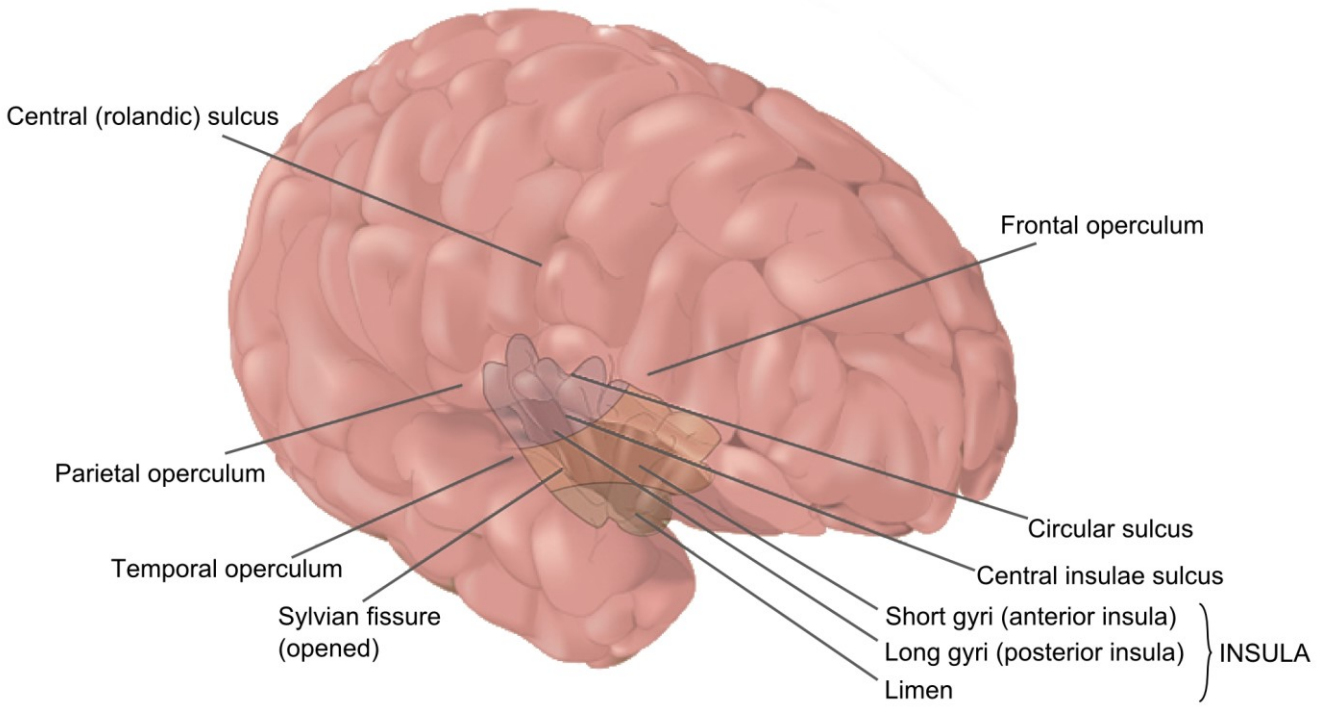

Figure 1. The insular cortex is a highly developed structure totally encased within the brain at the depths of the Sylvian fissure. Covered by the fronto-orbital, fronto-parietal, and the temporal opercula, it becomes visible only when the Sylvian fissure is widely opened. The oblique central insular sulcus, which parallels and often leads directly into the rolandic sulcus, separates the insular cortex into an anterior and posterior portion. The three (to four) anteriorly situated short gyri and the two posteriorly located long gyri form a fan like pattern, converging anteriorly and inferiorly towards the opening of this region (limen insulae).

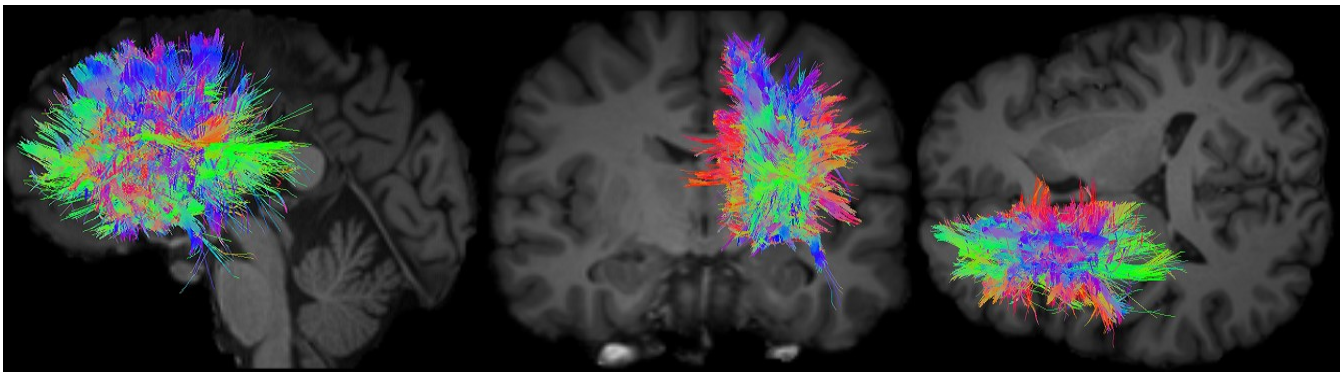

Figure 2a. Sagittal (left), coronal (middle) and axial (right) views of sample probabilistic tractography of the left anterior insula. Colors are in compliance with standardisation: inferior/superior, blue; anterior/posterior, green; left/right, red.

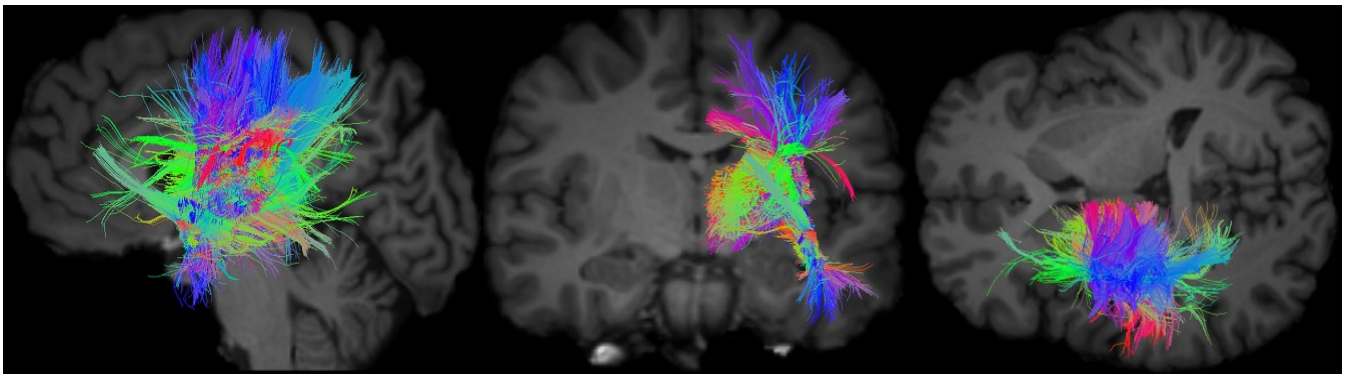

Figure 2b. Sagittal (left), coronal (middle) and axial (right) views of sample probabilistic tractography of the left posterior insula. Colors are in compliance with standardisation: inferior/superior, blue; anterior/posterior, green; left/right, red.

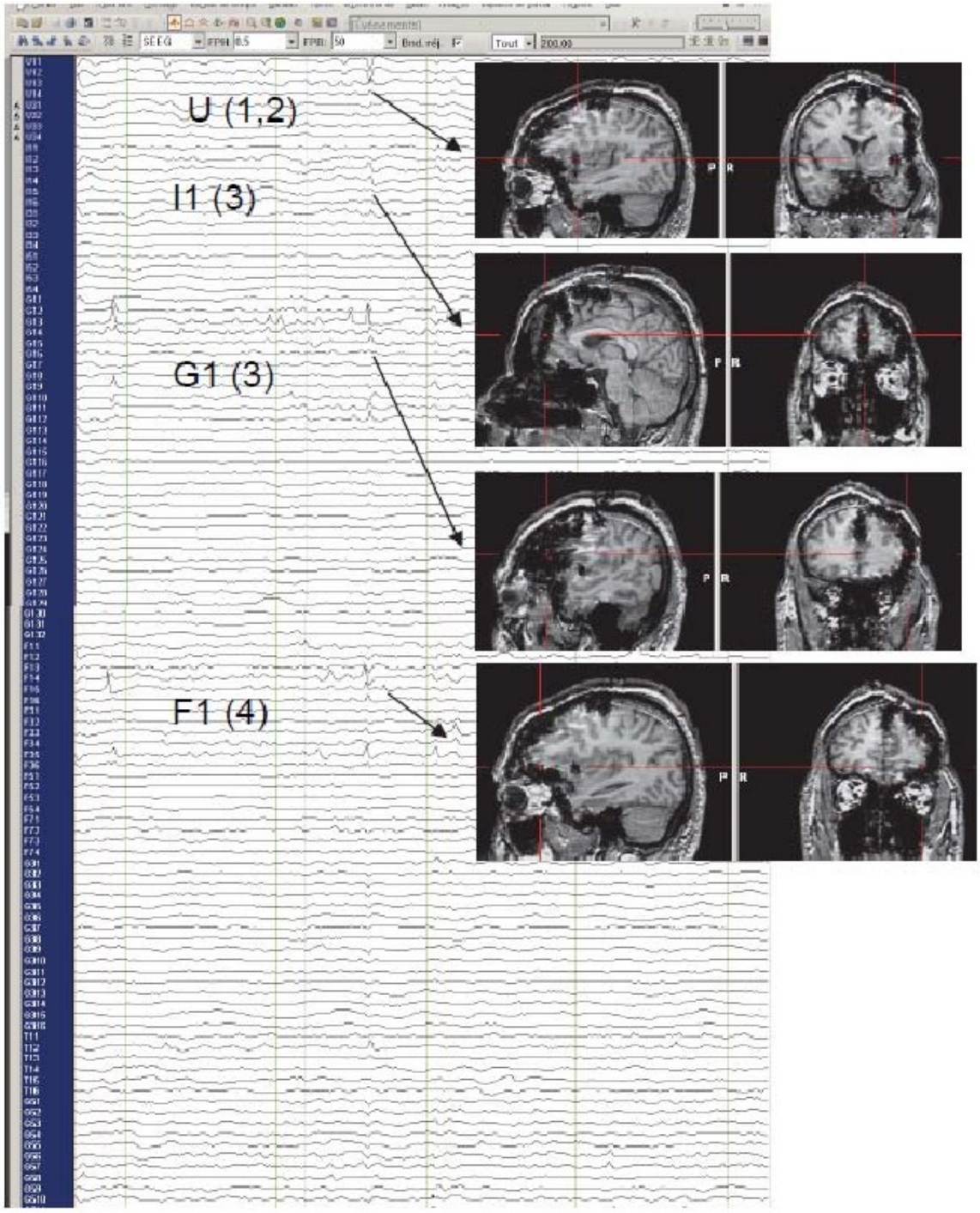

Figure 3. Example of a spontaneous spike recorded simultaneously over anterior insula [U1(1,2)], the lateral orbitofrontal cortex [F1(4)], the inferior frontal gyrus [G1(3)] and the posterior portion of the anterior cingulated gyrus [11(3)]

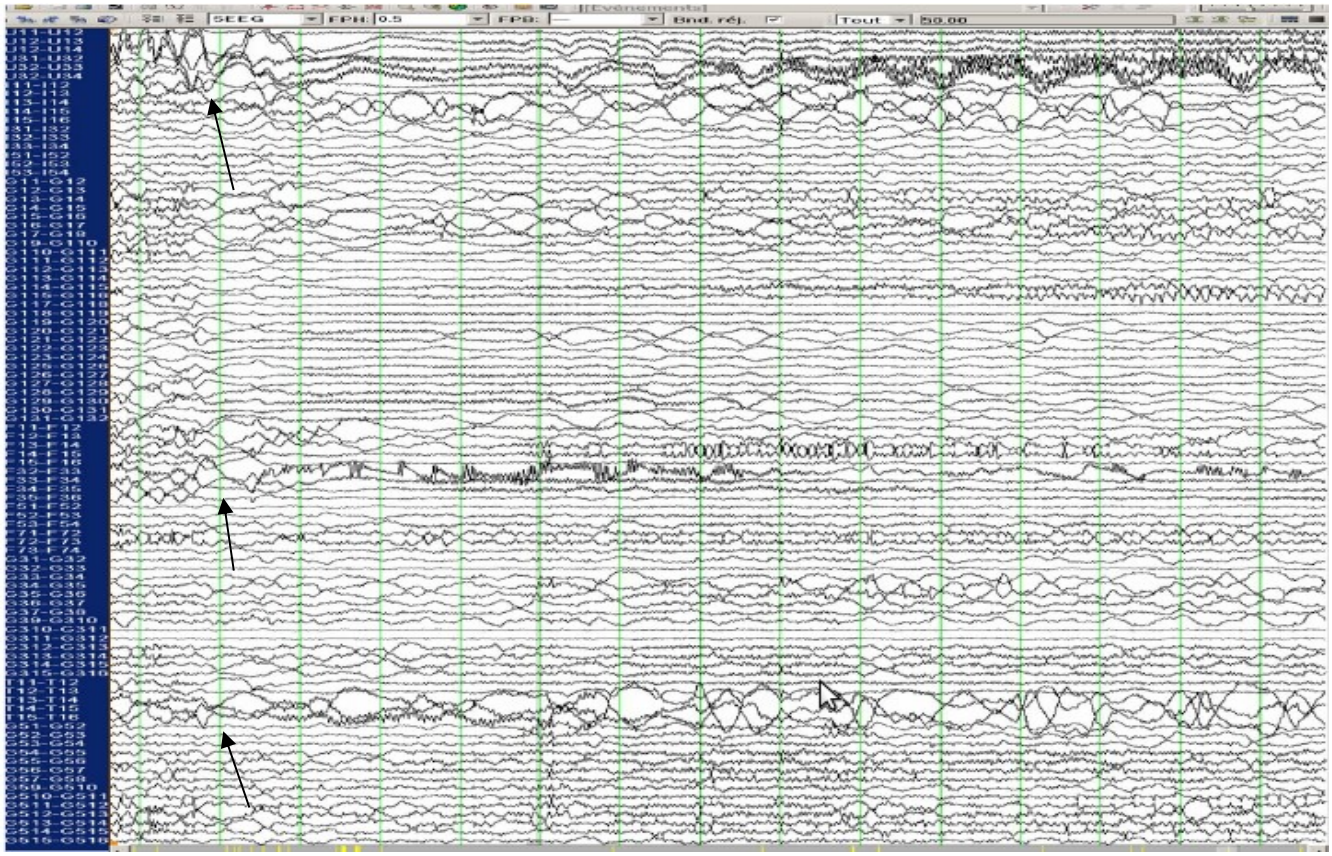

Figure 4. Start and buildup of a seizure originating from the insula. Note the complex electrophysiological picture with involvement of local and remote contacts (arrows).

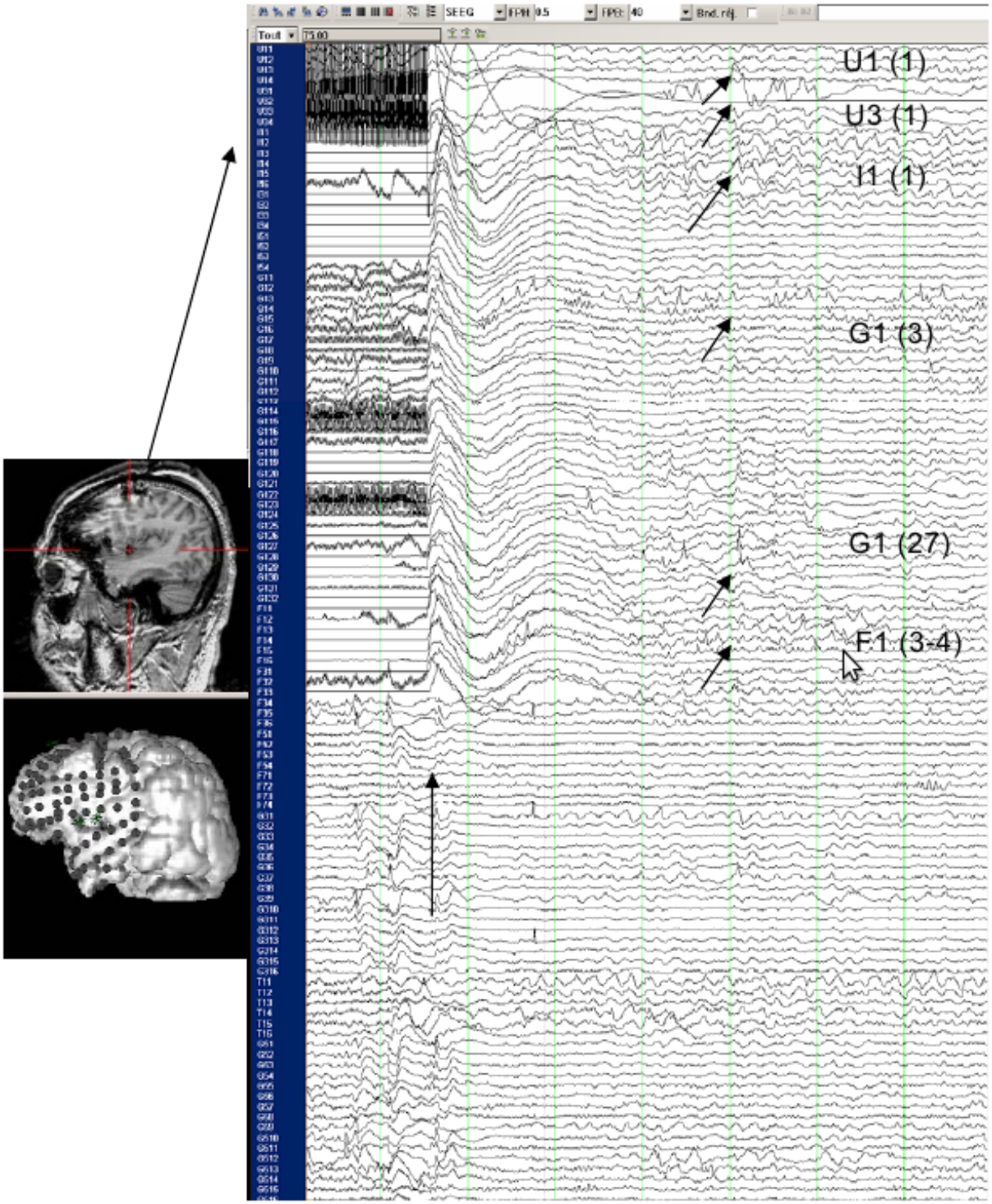

Figure 5. Electrical stimulation of the middle portion of the insula [U3 (1-2)] at 6mA generating after-discharges noted synchronously over close and distant contacts positioned in anterior insula [U1 (1)], the anterior medial frontal gyrus [I1 (2)], the inferior frontal gyrus [G1 (3,27)] and the orbitofrontal cortex [F1 (4)]

ANNEXE 2

Multimodal investigation of epileptic networks: The case of insular cortex epilepsy

Published by:

E. Rossignol, L. Carmant, & J.-C. Lacaille (Eds.), Neurobiology of epilepsy: From Genes to Networks. *Progress in Brain Research*. 2016 (vol. 226, pp. 1–33). Amsterdam: Elsevier.

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Abstract

The insula is a deep cortical structure sharing extensive synaptic connections with a variety of brain regions, including several frontal, temporal and parietal structures. The identification of the insular connectivity network is obviously valuable for understanding a number of cognitive processes, but also for understanding epilepsy since insular seizures involve a number of remote brain regions. Ultimately, knowledge of the structure and causal relationships within the epileptic networks associated with insular cortex epilepsy can offer deeper insights into this relatively neglected type of epilepsy enabling the refining of the clinical approach in managing patients affected by it.

In the present chapter, we first review the multimodal non-invasive tests performed during the presurgical evaluation of epileptic patients with drug refractory focal epilepsy, with particular emphasis on their value for the detection of insular cortex epilepsy.

Secondly, we review the emerging multimodal investigation techniques in the field of epilepsy, that aim to 1) enhance the detection of insular cortex epilepsy and 2) unveil the architecture and causal relationships within epileptic networks. We summarize the results of these approaches with emphasis on the specific case of insular cortex epilepsy.

Keywords: epilepsy, insula, connectivity, networks, multimodal, causality, neuroimaging

Epilepsy as a systems disease

For most epileptic patients (~70%), anticonvulsive drugs adequately control seizures. However, among the refractory cases, a significant proportion of patients are eligible for surgical treatment of seizures (Wiebe et al., 2001). The fundamental question in those cases is to localize the part of the brain that is responsible for patients' seizures, which constitutes the central thread of this chapter. Important advances in the surgical treatment of epilepsy arose from both a better formulation of this question and the development of methodological tools to answer it. Indeed, our notion of epilepsy has evolved from a local-based to network-based model, capitalizing on the ability of neuroimaging to study brain function at increasingly high spatial and temporal resolutions.

Early in the last century, the measurement of brain electrical potentials on the scalp by Berger paved the way for the investigation of the neuroelectric correlates of epileptic seizures. In addition to seizures, Berger also reported the existence of sharp electrical transients that are observable on the electroencephalogram (EEG) of epileptic patients in the absence of seizures. These "spikes" are usually observed on electrodes that record seizures but this is not always the case. This spatial distinction between the generators of seizures and spikes was further elaborated with the advent of intracranial EEG recordings (icEEG). IcEEG allows excellent spatial discrimination of the neural generators of epileptic activity, which led Laufs and Rosenow to propose a "zonal" model to explain the pathophysiology of epilepsy (Rosenow, 2001). The ''zonal'' model recognizes different zones associated with the clinical symptoms (symptomatogenic zone), the interictal spikes (irritative zone), the initiation of seizures (seizure onset zone - SOZ) and the functional deficits associated with the epileptic condition

(functional deficit zone). Importantly, they define an “epileptogenic” zone (EZ) that consists of the brain tissue that must be surgically resected for seizures to be cured. The spatial location of the EZ is usually estimated using multimodal investigation techniques, as will be described in the next section, but its true location can only be confirmed through positive surgical outcome.

Although the zonal concept of epilepsy had an important impact on the clinical management of epileptic patients, failure rates for epilepsy surgeries remain relatively important, as high as 30% for temporal lobe - TLE (Jeha et al., 2006; Wiebe et al., 2001) and 50% for frontal lobe - FLE (Jeha et al., 2007; Yun et al., 2006) and parietal lobe - PLE (Binder et al., 2009; D. W. Kim et al., 2004) epilepsy. In 2002, Spencer formulated the idea that we should envision generators of interictal and ictal activities as networks of structures rather than single zones (Spencer, 2002). Since the transition from interictal to ictal to postictal brain states occurs at the time scale of synaptic activity, this idea has 2 corollaries. First, it implies that the neural machinery supporting the emergence of epileptogenic networks (ENs) is hardwired into the brain (Richardson, 2012). Thus, epilepsy is a systems disease, the symptoms of which result from aberrant connectivity among a set of anatomical healthy structures (Avanzini and Franceschetti, 2003). Some authors suggest that neural networks are bistable systems that can exhibit both healthy and epileptiform activity for the same set of parameters (Breakspear et al., 2006; Da Silva et al., 2003; Marten et al., 2009). Dynamical transitions between these two states are called bifurcations, and the epileptic condition facilitates such bifurcations.

The second corollary is that network assembly is a highly flexible process; for a given set of components, there are a large number of network architectures, all of which may give rise to

different epileptiform activities and clinical symptoms. This idea has deep implications for clinicians and neuroscientists, since accurate localization of network components is insufficient for fully describing the pathophysiology of epilepsy. For such an endeavour, it is necessary to study time-varying network dynamics (Halász, 2010).

In order to illustrate the networks concept of epilepsy and the current techniques used in their investigation, we use the unique case of insular cortex epilepsy. The insula is a cortical structure located deep in the sylvian fissure and is hidden by the frontal, temporal and parietal opercula. Despite early reports on insular epileptiform activity (Guillaume and Mazars, 1949; Penfield and Faulk, 1955; Penfield and Jasper, 1954), insulectomy was not considered an efficient surgical approach (Silfvenius et al., 1964) until the past 15 years. Patient series from Isnard (Isnard et al., 2004) and Ryvlin (Ryvlin and Kahane, 2005) demonstrated that insular ENs include temporal, frontal and parietal structures and that the sequence of clinical symptoms associated with insular seizures can be explained by their patterns of propagation. Throughout this chapter, we will present multimodal investigation techniques used both for localizing the components of ENs and characterizing their architectures, with emphasis on insular cortex epilepsy (ICE). Part II presents the investigation techniques that are routinely used in most epilepsy centres for imaging the epileptogenic brain tissues. Part III presents new experimental investigation techniques that promise enhanced imaging and understanding of ENs.

Investigating the epileptic networks: clinical practice

Presurgical investigation techniques

icEEG

The gold standard in the localization of the anatomical components of epileptogenic networks consists of direct recordings of neuroelectric activity through electrodes in contact with brain tissue. IcEEG records local field potentials that are generated by neural populations within a 0.5-3mm radius from the tip of the electrode (Juergens et al., 1999; Mitzdorf, 1987), thus achieving the highest spatial resolution among all neuroimaging techniques used in clinic. The downside of such high resolution is obviously poor spatial coverage, since only a limited number of electrodes can be used without risking cerebral haemorrhage or neurological deficits (Wong et al., 2009). It is thus possible that the epileptogenic zone is not sampled by icEEG, leading to the wrong selection of surgical target. ICE provides an ideal illustration of this issue.

Insufficient insular coverage in patients with ICE was associated with a significant proportion of failed TLE, FLE and PLE surgeries. Initially, suspicions were raised by a study on patients with TLE with atypical clinical symptoms that were instead associated with insular activity (Aghakhani et al., 2004). Despite successive resections (up to 4) of anterior temporal, mesiotemporal and parietotemporal structures, patients continued having seizures. Unfortunately, no electrode sampled the insula in their study although insular hyperperfusion was clearly shown in one patient. The potential benefit from icEEG recordings in the insula in TLE was further demonstrated, as about 10% of patients diagnosed with TLE suffered from

ICE (Isnard et al., 2004). TLE-like symptoms in those patients were explained by secondary propagation of ictal activity to surrounding temporal structures. Similar conclusions were drawn by some studies on PLE and FLE (Roper et al., 1993; Ryvlin et al., 2006).

Based on these reports, our group lowered its decision threshold for insular implantations with depth electrodes in patients with non-lesional TLE, FLE and PLE. On a series of 18 patients meeting these criteria, we found that 40% patients who underwent icEEG recordings had seizures originating from the insula. In addition, electrical stimulation of the insula proved that insular epileptic discharges replicate semiology of various extra-insular epilepsies (Nguyen et al., 2009). Our findings, along with existing literature on this issue suggest that: 1) ICE is probably more prevalent than presently reported; more extensive studies must be conducted to determine its frequency, 2) despite extensive presurgical workups, non-lesional ICE is probably rarely detected, accounting for a significant proportion of failed epilepsy surgeries. We further review the different investigation techniques used in presurgical workups and discuss their value for detecting ICE.

EEG

EEG is probably the oldest and most widely used imaging modality in clinical investigations of brain pathologies, including epilepsy. Over the years, epileptologists developed expert skills in reading and interpreting EEG seizures, but also waveforms observed during the interictal state, such as spikes, polyspikes, spike-and-wave complexes, sharp waves, paroxysmal fast activity (Westmoreland, 1998) and high-frequency oscillations (Bragin et al., 1999). Advanced biophysical models and computerized techniques allow unprecedented

accuracy in the localization of those waveforms, as most advanced algorithms can theoretically reach a $10cm^2$ resolution (Grova et al., 2006), thus enabling "electrical source imaging" (ESI).

ESI relies on a biophysical model that relates neural electrical activity, modelled as a finite number of equivalent current dipoles (ECD), to electrical potentials recorded outside the head. We distinguish 2 broad classes of ESI techniques, according to the number ECD used for modelling brain activity. Single ECDs assume recorded electrical potentials are generated by a single (or a few) neural point source(s). Although this approach obviously oversimplifies neural generators and its numerical implementation requires strong heuristics (number of dipoles, initialization), it proved valuable in epilepsy when careful attention is paid to its limitations, as validated by simultaneous EEG and icEEG recordings (Boon et al., 2002; Ebersole, 1991; Roth et al., 1997). In general, all studies report usefulness of sECD for epilepsy, with sensitivity and specificity exceeding respectively 80% and 60% for the vast majority of studies (see Kaiboriboon et al., 2012 for a review).

In turn, distributed source modelling (DSM) models neural sources with a large number of ECDs homogenously distributed in the brain. Despite this mathematical challenge imposed by the large number of sources, DSM is increasingly being validated in the clinical management of epileptic patients, benefiting from increased head coverage of high-density EEG systems and increased accuracy of head modelling techniques. In the study with the largest cohort of patients, DSM was shown to accurately localize the onset of seizures, with sensitivity and specificity both exceeding 80% (Brodbeck et al., 2011), in line with several other reports (Michel et al., 2004; Sperli et al., 2006). In ICE, EEG was found to be insensitive to spikes

generated from the deep-seated insula, therefore we did not find any reports on the usefulness of ESI for that kind of epilepsy.

MEG

Magnetoencephalography (MEG) is a relatively new imaging modality that records the magnetic fields generated by electrical currents flowing inside active neurons. Despite a relatively short history of clinical investigation and higher operation costs than EEG, MEG has quickly established itself as an important tool in presurgical evaluation of epilepsy. Owing to the relatively simpler physics of neural magnetic fields propagation, MEG is sensitive to smaller activated brain regions (~4cm^2 for MEG - Mikuni et al., 1997, ~10cm^2 for EEG - Grova et al., 2006). Source localization with DSM showed promising results for the presurgical workup of epilepsy, which led some authors to suggest that it could obviate icEEG investigations in some cases (Fujiwara et al., 2012).

Several studies demonstrated the usefulness of sECD modelling with MEG on different types of epilepsy. Globally, the reported accuracy of sECD is above 75% for the majority of the studies (Knowlton, 2006; Minassian et al., 1999; Stefan, 1993). In addition, MEG was also shown to be valuable for appropriately determining the subsequent icEEG coverage zone (Mamelak et al., 2002; Fischer et al., 2005; Knowlton et al., 2009). Unfortunately, only a few studies report sECD investigation of insular cortex epilepsy. Among those, Heers et al. studied 3 patients with cryptogenic epilepsy and hypermotor seizures (Heers et al., 2012). They showed that MEG can not only identify epileptic foci when other modalities fail but is also able to localize deep-seated foci such as in the insula (Park et al., 2012). We recently

investigated 14 patients with insular seizures using MEG. Among those, localization of interictal spikes showed clear insular or perisylvian focus in all but one patient. Taken together, these studies suggest that MEG is valuable for detecting ICE.

In turn, we found substantially fewer reports of DSM, probably due to the fact it is more recent and less validated. Nonetheless, studies using DSM advocate for its more extensive use in presurgical workups since it outperformed sECD in at least 2 comparative studies (Shiraishi et al., 2005; Tanaka et al., 2009). It was also shown that patterns of source activity reconstructed with DSM were good predictors (up to 94%) for subsequent surgical resection (Tanaka et al., 2010).

MRI

Magnetic resonance (MR) scanners exploit the intrinsic magnetic properties (the spin) of electrons to produce high-resolution images of brain (and body) tissues. Using a sophisticated combination of spin polarization and perturbation, MR imaging (MRI) now allows recovering the 3-dimensional properties of the brain with 1mm resolution. MRI is an essential tool in the evaluation of patients with focal epilepsy, allowing the visual detection of a variety of epileptogenic brain lesions such as gliosis from acquired insults, tumors, vascular malformations or malformations of cortical development. Globally, the sensitivity of MRI in epilepsy surgery candidates ranges between 75% and 86% (Bronen et al., 1996; Brooks et al., 1990; Cascino et al., 1992; Grattan-Smith et al., 1993; Kuzniecky et al., 1993; Laster et al., 1985; Latack et al., 1986; Ormson et al., 1986; Scott et al., 1999).

Literature on insular cortex epilepsy provides contrasting results with respect to the sensitivity of MRI. We found 6 studies in which all patients (N = 43) displayed some abnormality (Cukiert et al., 1998; Duffau et al., 2002; Heers et al., 2012; Kaido et al., 2006; Roper et al., 1993; von Lehe et al., 2008), 2 studies (N = 23) with both MRI-positive and MRI-negative patients (Malak et al., 2009; Mohamed et al., 2013) and 7 studies (N = 19) with exclusively MRI-negative patients (Dobesberger et al., 2008; Isnard et al., 2004, 2000; Kriegel et al., 2012; Nguyen et al., 2009; Ryvlin et al., 2006; Zhang et al., 2008). Overall, MRI had a sensitivity of 61%, corresponding to 87% positive predictive value when considering the results of surgery. Overall, our short review suggests that MRI is a highly valuable tool for investigating ICE with moderate sensitivity but excellent diagnostic value. However, the relatively larger number of patients diagnosed with lesional rather than non-lesional ICE might reflect the fact that non-lesional ICE is a poorly diagnosed disease, and that currently available investigation tools other than MRI have low diagnostic value for this disease.

PET

Positron-emission tomography (PET) measures the concentration of a specific source of radiation in the 3D space. The brain property imaged with PET thus depends on the choice of an appropriate radioligand, such that 3D concentrations can be interpreted in terms of brain function. In epilepsy, 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose (FDG) and [^{11}C]-flumazenil (FLU) are two complimentary and commonly used radioligands, imaging brain function (glucose consumption) and structure (neuronal loss), respectively. The epileptic condition is associated with neuronal loss and, paradoxically, decreased concentrations of FDG in affected brain

regions. Although this last observation is largely consensual, the underlying neurophysiological mechanisms are still not understood.

Studies comparing FLU- and FDG-PET for localizing the brain regions involved in epileptogenic networks report similar performance of both molecules for most groups of patients. Globally, these two modalities achieve similar sensitivity and specificity (Ryvlin et al., 1998) and are equally predictive with respect to surgical outcome (Debets et al., 1997). It was noted however that the only cases where FLU-PET added new information above that of MRIs are when FDG-PET is negative, which implies that FDG-PET should be performed first, and FLU-PET only when FDG-PET is negative.

Since the role of insula has only gained recognition in the last 10 years, early PET studies reporting changes in metabolism in the insula did not include insular intracranial electrodes (Bouilleret et al., 2002; Didelot et al., 2008; Hur et al., 2013; Joo, 2005; Wong et al., 2010). For this reason, although they provided interesting insights into the involvement of the insula in the metabolic changes associated with TLE, they are inconclusive with regards to ICE. We found few reports of ICE with icEEG and PET data (Dobesberger et al., 2008; Heers et al., 2012), including 2 studies from our group (Nguyen et al., 2009; Surbeck et al., 2014). Pooled together, these studies suggest that FDG-PET has low sensitivity (17%) and specificity (53%) to insular cortex epilepsy.

SPECT

Single-photon emission computerized tomography (SPECT) consists in localizing the source of gamma-ray emission within the brain. The source consists of a radioactive tracer

(usually the 99mTc-labelled HMPAO - hexamethylpropyleneamine oxime) bound to a molecule that freely crosses the blood-brain barrier, such that it diffuses into the brain after intravenous injection. Since the tracers used in SPECT have relatively long half-lives, they distribute spatially in brain regions with higher blood flow and remain stable for up to a few hours. Patients can thus be EEG-video monitored and injected at the time of a relevant brain activity (ideally seizure onset) as seen on the EEG traces. It is generally agreed that the use of SPECT during interictal brain state is of limited use (Debets et al., 1997; Lascano et al., 2015; Spencer, 1994). In contrast, SPECT is mostly useful when the radioligand is injected at seizure initiation (Joo et al., 2004; Spencer, 1994). In addition, even better results can be achieved by subtracting interictal from ictal SPECT images, a technique called SISCOM. Such an operation is especially useful in cases where ictal hyperperfusion is low in epileptogenic zone due to superposition on a preceding hypoperfused state (Desai et al., 2013; Newey et al., 2013; Spencer, 1994; von Oertzen et al., 2011).

As for PET, there are only a few studies that reported on the value of SPECT in insular cortex epilepsy. We found few reports of ICE with icEEG and PET data (Dobesberger et al., 2008; Heers et al., 2012), including 2 studies from our group (Nguyen et al., 2009; Surbeck et al., 2014). Pooled together, these studies suggest that SPECT has low sensitivity (23%) and specificity (48%) to insular cortex epilepsy.

Illustrative case

A 10-year-old ambidextrous girl with mild language delay started having seizures at the age of four years characterized by an unpleasant tingling sensation in the lower back, right

arm and both legs followed by fear and complex motor behaviors. Seizures became predominantly nocturnal after a few weeks and have remained so since, recurring in clusters of 4 or 5 (up to 15) every 2 to 3 days. After failing six adequate antiepileptic drug trials, the patient was referred for epilepsy surgery. While the clinical history might have suggested a frontal lobe focus, video-EEG monitoring revealed right temporal, central or centro-temporal discharges interictally and right centro-temporal rhythmic activity at seizure onset (Figure 1). High-resolution 3Tesla brain MRI and volumetric studies failed to disclose an epileptogenic lesion. Interictal FDG-PET was normal but ictal SPECT showed increased cerebral blood flow over the right insular region (Figure 2). Source localization of interictal epileptiform discharges recorded during magnetoencephalography (CTF 275-sensory system, Canada) using an electrical current dipole model revealed a concordant tight cluster at the very posterior end of the right Sylvian fissure (posterior insula and parietal more than temporal opercula – Figure 3). During spikes, combined EEG-fMRI recordings showed (BOLD) activations over the right posterior insula, the overlying perisylvian cortex but also in central regions and the cingulate gyrus (Figure 4). Functional MRI for language suggested left-hemisphere dominance. Based on this multimodal non-invasive evaluation, epilepsy surgery was recommended. With the removal of the right parietal operculum, temporal operculum and posterior insula, seizure-freedom was attained (follow-up 2 years).

Investigating the epileptic networks: perspectives

Advanced localization techniques

EEG/MEG fusion

Both EEG and MEG directly address neuronal activity by recording differences in electrical potentials and magnetic fields respectively, outside the head. Although both modalities record activity from the whole brain, they are preferentially sensitive to different populations of neurons. Indeed, EEG is mainly sensitive to radially oriented sources lying on cortical gyri since they are closer to the sensors while the magnetic fields generated by those sources vanish due to the quasi-spherical head shape. In turn, MEG is mainly sensitive to tangential source lying along the sulci walls (Ahlfors et al., 2010; Sharon et al., 2007). Thus a cortical region participating in an EN would only be partially recovered by EEG and MEG if it extends spatially from the top of a gyrus to a cortical fold. Some studies further observed noticeable epileptogenic activity on one modality but not the other (Barkley and Baumgartner, 2003; Iwasaki et al., 2005), highlighting the need for simultaneous EEG-MEG recordings. Importantly, it was shown that EEG and MEG acquired simultaneously are super-additive, i.e. they provide more information relevant to source localization than the sum of unimodal information (Pflieger et al., 2000).

Simultaneous EEG/MEG (MEEG) recordings were introduced in epilepsy with the aim to better delineate the location and spatial extent of cortical sources participating in epileptogenic networks. Using simulations of realistic epileptic spikes, Chowdhury et. al. showed that MEEG provides better localization than EEG or MEG alone, regardless of the inversion scheme used (Chowdhury et al., 2015). However, contrary to what is commonly believed they

showed that the Maximum Entropy on the Mean framework (Amblard et al., 2004) not only provides the most accurate localization of the simulated sources but is also able to recover their spatial extent (Chowdhury et al., 2013), (Ebersole and Ebersole, 2010). In addition, in the same study on two patients with frontal lobe epilepsy, MEEG was able to track interictal spike propagation patterns while individual modalities were insensitive to spatiotemporal dynamics of the spikes. Similar conclusions were drawn from a recent study comparing unimodal and multimodal MEEG source localizations with intracranially-recorded EEG on a patient with multifocal refractory epilepsy. The authors show that MEEG is able to recover most of the regions participating in the generation of spikes, even when no single modality was able to recover them (Aydin et al., 2015). This study illustrates the supra-additive nature of MEEG and its potential to recover more components of ENs.

We recently started exploring the potential of MEEG source imaging of epileptic spikes to detect insular activations in ICE. Extending the previously cited reports, we found that EEG and MEG are each able to detect insular activations on subsets but not all spikes. However, MEEG source imaging provided more robust results and could detect insular activations in cases where only a single modality was positive (see figure 5a) and even when both modalities were negative (figure 5b). These preliminary results suggest that MEEG source imaging of epileptic spikes is a promising avenue for the computer-assisted detection of ICE.

Combined EEG and fMRI

A clinical-grade MR magnet is probably among the most hostile environments for recording scalp potentials with EEG. Indeed, even small movements of the EEG electrodes

inside the scanner as a result of small head movements or ballistocardiographic effects, translate into current induction in electrodes. In addition, the on/off switching of the radiofrequency antennas creates even larger artifacts on the EEG, two orders of magnitude larger than the activity of interest. Nonetheless, modern signal processing techniques allow for a proper cleaning of EEG data such that EEG-fMRI can be used for relating haemodynamic and neuroelectric brain activity. Given the deterministic nature of the gradient artefact, waveform averaging was introduced (Allen et al., 2000) and validated (Gonçalves et al., 2007; Salek-Haddadi et al., 2002) to subtract the artefact from the EEG. Other filtering techniques, applicable to the ballistocardiographic effect, were also proposed based on spectral domain filtering (Sijbers et al., 1999), wavelet filtering (K. H. Kim et al., 2004), spatial Laplacian filtering, PCA (Niazy et al., 2005) and ICA (Mantini et al., 2007; Srivastava et al., 2005).

In the context of epilepsy, one of the most widely used EEG-fMRI paradigms is to analyse the blood oxygen level-dependent (BOLD) signal in an event-related design where the events are EEG-marked interictal spikes. After preprocessing, spikes are marked on the EEG by expert epileptologists. The EEG signal is then binarized according to the spike marking, downsampled to match fMRI time resolution, and convolved with a model of the haemodynamic response function that is then cast as a regressor in the general linear model. The most common model is the canonical haemodynamic response function (HRF), which accounts for local elastic deformation of blood capillaries and the resultant transient increase in local blood oxygenation in response to neuronal activity - also termed neurovascular coupling (Buxton et al., 1998). However, it was shown that the shape and onset of the HR can vary significantly among subjects (Aguirre et al., 1998; Lindquist et al., 2009), with respect to:

subjects age (D'Esposito et al., 1999; Jacobs et al., 2008), brain regions (Handwerker et al., 2004) and brain lesions including epileptogenic lesions (Lemieux et al., 2008; Masterton et al., 2010). Several alternate models of the HRF were proposed to account for such variability, including general non-linear fits of the HRF, multiple HRFs with varying onset and peak times, HRF along with its time-derivatives (Friston et al., 1998), general basis functions sets (Josephs and Henson, 1999) and the superposition of three inverse logit functions (Lindquist et al., 2009). These models are then integrated in a general linear model to infer the response of each voxel to the epileptic activity (Friston, 1995). Irrespective of the chosen model, usefulness of EEG-fMRI to imaging epileptic networks has been demonstrated in several studies.

First, it was shown that the BOLD signal provides useful information for confirming the location of the suspected epileptic focus. Depending on the study, proportions of patients who display IED-related changes in the BOLD signal ranged from 67% to 83% (Kobayashi et al., 2006; Salek-Haddadi et al., 2006). The most clinically useful BOLD changes are activations, since identification of a single activation cluster was found to be concordant with electro-clinical symptoms in over 80% of cases (Krakow, 1999; Salek-Haddadi et al., 2006; Thornton et al., 2010) and are good predictors of positive surgical outcome (An et al., 2013). Importantly, a number of studies showed that EEG-fMRI has the potential to reveal the components of ENs. Indeed, in mesial TLE, BOLD occasionally displays significant activation clusters in the contralateral temporal and extratemporal regions (Avesani et al., 2014; Kobayashi et al., 2006; Tousseyn et al., 2014). Those clusters were considered as patterns of spike propagation since surgical outcomes are good despite sparing those clusters. Similarly,

in patients with intractable generalized epilepsy (IGE) whose interictal activity is characterized by sharp spike-wave bursts, BOLD changes show significant activation of the thalamus while EEG does not (Aghakhani, 2004).

We recently conducted an EEG-fMRI study aimed at revealing the EN associated with ICE (unpublished results). We recruited 13 ICE patients, as confirmed by surgical outcome after insulaectomy. We were able to detect IEDs in 62% of patients, similarly to what has been reported in studies on other kinds of epilepsies. We found ipsilateral insular and or perisylvian BOLD activations in 6 patients while the remaining two displayed significant BOLD activation in the contralateral insula (data from 1 patient is shown in Figure 4). In addition to insular and perisylvian activations, significant BOLD clusters were found in the post-central gyrus, superior parietal lobule, middle or superior frontal gyri and anterior cingulate or medial frontal gyri, all of which were previously shown to share structural connectivity with the insula (Augustine, 1996; Nieuwenhuys, 2012). We thus think that EEG-fMRI is a promising tool for revealing complex ENs in ICE.

Quantified icEEG

In principle, icEEG recordings are the gold standard in epilepsy as they allow for direct sampling of epileptogenic brain regions, assuming coverage is appropriate. Localization of the seizure onset zone thus amounts to identifying the first contact displaying epileptiform activity at seizure initiation. However, such activity often appears nearly simultaneously on a number of contacts and visual identification of relevant nodes of the EN is a challenging task. Thus,

some strategies were proposed for automatically labelling the most important contacts at seizure initiation.

By combining spectral and temporal information at seizure onset, Bartolomei et al. introduced an empirical index that measures the propensity of each node to initiate seizures (Bartolomei et al., 2008). More specifically, they computed a ratio of energy of high frequencies (beta and gamma) over lower frequency bands (delta, theta, alpha) at each time bin of the time-frequency decomposition of EEG signals. This ratio is then normalized and cumulated over time in what is called the "energy ratio" function. When a seizure is recorded, this function contains a local maximum at seizure onset, and the amplitude and latency of that maximum are used to define the so-called "epileptogenic index" (EI), which measures the involvement in seizure initiation.

The EI proved useful for the study on epileptogenic networks, especially in mesial TLE. Indeed, the number on nodes with high EI was higher for patients with identified lesions than for patients with normal MRI, which was an important predictor of surgical outcome (Bartolomei et al., 2008). In addition, the EI captures some subtleties in the clinical symptomatology of patients, since it can be used to classify patients with clinical subtypes of mesial TLE (Bartolomei et al., 2010) and discriminate patients with mesial MTLE from those suffering from other types of TLE (Vaugier et al., 2009).

Neuroimaging brain networks

Networks can be schematized as a set of nodes connected to each other through specific links called edges. Nodes and edges are the workhorse of a large research community

studying networks, ranging from air traffic, power plants to brain networks. In neuroscience, network analyses answer 2 broad categories of questions: 1) how does edge strength between a given node and a set of other nodes evolve with respect to experimental paradigm and 2) how do the global features of networks evolve with respect to experimental paradigm?

The main challenges here consist in defining relevant nodes and edges. Many approaches were proposed for designing nodes encompassing random, data-driven and atlas-based strategies. We note that atlas-based strategies provide regions of interest (ROIs) that are more easily interpretable in terms of neurophysiology as they allow for the understanding of neural systems in terms of associations of broadly specialized functional units. Edges represent the strength of the connectivity between two nodes, and their interpretation depends on the imaging modality. Briefly, we distinguish 3 types of connectivity: functional, effective and structural. Functional and effective connectivity are measures of undirected and directed statistical coupling among signals, respectively, and must be estimated using multivariate time series (EEG, MEG, fMRI). In turn, structural connectivity is defined in terms of anatomical association between ROIs such as fiber tracts density and is usually estimated through diffusion imaging. One can analyse the values of edges linking a specific set of nodes, also called “seeds”. Those seed-based analyses were carried out in a wide variety of epilepsy types, encompassing “focal” and “generalized” types. In those analyses, variations in edge values are assessed with respect to experimental paradigms, allowing the interpretation of pathophysiology and clinical symptoms in terms of brain connectivity. A sample of those studies is described in the following sections with respect to imaging modalities.

The complete graph of connections between all available nodes is called a “connectome” and analyses of such graph are thus termed “connectomics”. This field of mathematics was originally framed into the so-called “graph theory”, which recently raised spectacular interest in neuroscience in general, and epilepsy in particular. Graph theory provides a variety of metrics that describe interpretable features of connectomes, such as the clustering coefficient, which indexes the tendency of nodes to form “cliques” with dense internal connections, and the average path length, which measures the average number of relays while trying to go from one node to another. Strikingly, many networks, including brain networks, were found to have relatively high clustering coefficient and low average path length. Those “small-world” networks share fast processing of information within functional units through dense local connections and the ability to parallelize information processing through sparse but efficient long-range connections (Watts and Strogatz, 1998). In epilepsy, metrics such as “small-worldness”, efficiency and modularity shed new light on the large-scale neurophysiological mechanisms at play during interictal and ictal states.

EEG/MEG connectivity

Definition of nodes and edges in EEG and MEG is usually done in the sources space since each EEG electrode and MEG sensor records mixtures of neural signals from a large portion of the brain, which implies that connectivity in the sensors spaces has little interpretability with respect to underlying neural generators (but see Holmes et al., 2010; Horstmann et al., 2010; van Mierlo et al., 2014 for interesting reports on functional connectivity on the sensors). In the majority of studies, DSM is done using thousands (~10k)

of ECDs and connectivity analyses at such resolution is impracticable for two reasons: 1) the computational cost increases exponentially with the number of sources and 2) the spatial resolution of ESI/MSI is much lower than that of the head model, which implies that neighbouring sources are heavily cross-contaminated. The most common strategy to address these two issues is to perform space reduction by pooling (Hillebrand et al., 2012; Tana et al., 2012) source signals into ROIs, which are then taken as the nodes of the connectome. Connectivity among ROIs can then be evaluated using various metrics, all of which have specific strengths and weaknesses and they all display acceptable performance in the majority of cases (Wendling et al., 2009).

When analyzing interictal discharges, few studies showed that functional connectivity provides useful diagnostic information about the epileptic networks of patients and even for surgical outcome prediction. Using ESI of interictal spikes and a time-varying frequency-resolved effective connectivity metric, Coito et al. found dissociation in the pattern of connectivity between patients with left and right TLE (Coito et al., 2015). Indeed, the latter exhibited increased contralateral connectivity, in line with contralateral frontal functional deficits in right TLE. In addition, effective connectivity on MEG data showed that surgical resection of the main driving nodes of ENs could predict favourable outcome in 9/10 patients (Dai et al., 2012; Jin et al., 2013). However, definite conclusions about outcome prediction are limited by the fact that those studies did not include cases with negative surgical outcome. Similarly, Malinowska et al. showed that MEG-identified network drivers showed good concordance both with drivers identified from icEEG and with resected areas (Malinowska et al., 2014).

Our group recently conducted a MEG study aimed at studying functional connectivity networks at play during interictal insular spikes (Zerouali et al., submitted). We computed the connectomes of insular spikes using MSI based on the Maximum Entropy on the Mean algorithm and phase-synchronization measures and conducted seed-based connectivity analyses. We showed that anterior and posterior parts of the insula are characterized by markedly distinct connectivity networks, with the former connected mainly to anterior structures while the latter is mainly connected to parietal and occipital structures (Figure 6). In this study, we showed that MEG is able to establish a robust signature of ICE based on functional connectivity measures, which could open important avenues in the automatic detection of ICE.

Other studies analysing seizures showed that transitions between brain states display deep modifications in connectivity. Using EEG and Granger causality, Coben et al. showed hyperconnectivity at the transition between ictal and postictal states (Coben and Mohammad-Rezazadeh, 2015). In addition, according to Elshoff et al., the pattern of connectivity at seizure initiation is entirely driven by a single node then becomes circular around the middle of seizures (Elshoff et al., 2013). They also showed that surgical resection of the main driving node at seizure initiation yielded a positive outcome (8/8) while the opposite yielded a negative outcome (3/3) for patients. Interestingly, topological features were also shown to vary at those transitions. Using frequency-resolved connectivity, Gupta et al. showed that transition from preictal to ictal ictal states display networks with increased “small-worldness”, which suggests seizure initiation necessitates more ordered network structure (Gupta et al., 2011).

fMRI connectivity

Early seed-based connectivity studies using fMRI were conducted during rest sessions, where healthy subjects are instructed to avoid focusing on any particular thoughts. Using such paradigm, Biswal et al. showed that bilateral motor cortices are not silent but rather exhibit strong connectivity at rest, which suggests that these regions continue sharing and processing information offline (Biswal et al., 1995, 1997). Later, other studies showed that large-scale brain connectivity at rest is rather the norm than the exception, and a number of networks were found to be highly consistent across subjects and experiments (see Fox and Raichle, 2007 for a review). These resting-state networks are now well established as robust signatures of healthy brain functioning.

Seed-based analysis was applied to study the functional connectivity of the human insula, revealing 2 main insular clusters, one anterior and one posterior. The anterior portion of the insula (aI) was found to be connected to the anterior cingulate cortex (ACC), the anterior and posterior parts of the middle cingulate cortex (MCC) while the posterior portion of the insula (pI) was found to be connected only to the posterior MCC (Taylor et al., 2009). In addition, the aI is functionally connected to the middle and inferior frontal cortex while the pI is connected to the primary and secondary somatosensory and the supplementary motor areas (Cauda et al., 2011). Some studies refined this parcellation, showing that aI can be subdivided into ventral and dorsal aI, each having specific patterns of functional connectivity with the cortex (Deen et al., 2011). In addition, this tripartite parcellation is supported by the distinct involvement of those 3 regions into specific cognitive tasks (Chang et al., 2013). However, to our knowledge, no study has linked these specific connectivity networks to epileptic activity in

ICE. Such studies are needed to shed some new light on the pathophysiological mechanisms of that disease, as was done for other kinds of epilepsies.

Structural connectivity

The anatomical connections linking neural populations can be studied in vivo using Diffusion weighted imaging (DWI). This modality exploits information about the diffusivity of molecules (mostly water) in the brain tissue. Mathematical models were proposed to translate this information into 3D images of white fiber tracts. In general, these models assume that water diffusivity in the brain is constrained by cellular structural elements such that it has preferential directions, which can be estimated in the form of fractional anisotropy (FA). For instance, water diffuses much more freely along than across the axon, thus a voxel crossed by an axonal bundle would have a high FA. Importantly, by tracking the FA along consecutive voxels, thereby performing tractography, it is possible to reconstruct the major white fiber tracts of the brain (Jbabdi and Johansen-Berg, 2011; Le Bihan, 2003; Mori et al., 2002).

To our knowledge, only three studies used tractography to investigate the structural connectivity of the insula. They report comparable connectivity profiles showing that the anterior insular cortex has connections mostly with frontal and temporal (inferior and superior gyri, amygdala) structures. The middle insular cortex has connections with frontal (superior, inferior, precentral), parietal (postcentral, supramarginal) and temporal (inferior, superior) gyri. Finally, the posterior insular cortex has connections with frontal (superior, inferior, precentral), parietal (postcentral) and temporal (inferior and superior) gyri and with the putamen (Cerliani et al. 2012; Cloutman et al. 2012; Jakab et al. 2012). These results are in

accordance with tract-tracing studies but some connections in primates were not found in humans. Using state-of-the-art tractography, our group further investigated the structural connectivity of the human insula and found many previously missed connections, such as those with the cingulate, parahippocampal, supramarginal, angular and lingual gyri as well as the precuneus, cuneus and occipital cortex (Ghaziri et al. 2015, submitted).

Tractography can also be used to study white matter insults in relation to epilepsy (for a review see Anastasopoulos et al., 2014; Ciccarelli et al., 2008; Winston, 2015). Studies generally report a FA decrease and a mean diffusivity increase in pathways near the epileptogenic temporal lobe (e.g. optic radiations, uncinate and arcuate fasciculi, cingulum, fornix and external capsule), which reflects reduced axonal density in TLE. White matter insults in TLE are mostly ipsilateral to the SOZ and tracts closely connected to the affected temporal lobe are the most disturbed. Furthermore, fiber tracts remote from the temporal lobe are also affected, which supports the view of epilepsy as a brain network disease (Concha et al., 2012; Gross, 2011; Otte et al., 2012; Rodríguez-Cruces and Concha, 2015). To follow-up on our study on healthy controls, we performed tractography on patients with ICE. Using non-parametric statistical tests, we assessed the differences between each patient and controls in fiber tract density linking the insula to the remaining cortex. Although preliminary, our results suggest that anterior, posterior and inferior ICE differentially affects the white fiber tracts, which could open new perspectives in the diagnosis of this kind of epilepsy.

icEEG connectivity

The main specificity of icEEG as compared to EEG/MEG connectivity is the sparse sampling of neural generators, and coverage extent is determined by balancing the amount of diagnostic information and health risks for patients. For that reason, it is usually agreed that icEEG connectivity only allows partial assessment of the brain connectome. However, judicious choice of epileptic cases in conjunction with the optimized placement of electrodes allows for characterizing the most relevant aspects of ENs. Indeed, most of the studies we describe below are conducted on patients with focal seizure onsets and limited propagation, such that the EN can mostly be sampled with intracranial electrodes.

Since the introduction of the network concept of epilepsy in the early 2000s, a large research effort was devoted to characterizing neural synchronization related to the epilepsy. The unequivocal findings of such research are that: 1) from a static point of view, the epileptic condition is characterized by deep impacts on large-scale neural synchronization and 2) the most spectacular changes in neural synchronization are related to brain dynamics, i.e. occur at transitions between consecutive brain states before, during and after seizures. In the following, we discuss the literature relative to those two findings separately.

Static network properties. In order to study the impact of the epileptic condition on brain networks, the most common paradigm consists in using artefact-free rest EEG data. Using such data, two independent studies showed that patterns of neural synchronization characterize distinct groups of epileptic patients. Ortega et al. analysed ECoG data from 29 patients with TLE and computed 3 synchronization measures in a short time frame sliding over continuous recordings (Ortega et al., 2008). They showed that synchronized ECoG contacts can either

spread over the whole lateral temporal lobe or cluster tightly in specific subregions. Importantly, they found that the predictive value with respect to seizure-freedom after surgery (Engel Ia) was very high and very low for tight and diffuse synchronization clusters, respectively. This suggests that synchronization patterns can be used to identify regions participating in seizures.

In addition to spatial patterns, synchronization strength was also shown to predict surgical outcome. In a series of 29 patients with TLE, Antony et al. assessed synchronization strengths among EEG signals recorded with intracerebral electrodes at rest. They showed that patients with low connectivity strength had better surgical outcome than patients with high connectivity strength, and that the linear classifier was able to accurately classify those two groups of patients based on the average and standard deviation of global synchronization (Antony et al., 2013). The idea that decreased levels of synchronization might be characteristic of the epileptic condition received further support when Warren et al. (2014) compared synchrony at rest between epileptic patients and controls with intracranial electrodes implanted for treating intractable facial pain. Controlling for inter-contact distance, synchrony levels between patients and controls were either decreased or increased depending on the frequency band analysed. However, finer analysis revealed that synchrony between the SOZ and other brain regions is significantly weaker than in controls, while synchrony either within SOZ or outside SOZ was unchanged (Warren et al., 2010). Further insights into the role of synchrony in epilepsy were provided by studies of seizure dynamics.

Network dynamics: synchrony. In order to study temporal evolution of synchrony levels, Wendling et al. recorded seizures with icEEG in 10 patients with focal epilepsy. Comparing

global synchrony levels (as measured with a linear correlation coefficient), they showed that seizure initiation displays large decreases in synchrony as compared to pre-ictal and post-ictal states (Wendling, 2003). In another study on patients with medial TLE, Mormann et al. showed that synchrony levels between bilateral hippocampi are markedly decreased before seizure onset and return gradually to baseline levels as seizure unfolds (Mormann et al., 2003). Interestingly, in 8 out of 10 patients, they were able to accurately predict seizures by detecting pre-seizure state based on reported lower synchronization values.

In addition, some authors tracked synchrony levels in epileptic networks along seizures. Using icEEG recordings from 11 patients with focal epilepsy, Kramer et al. performed temporal normalization for aligning seizures from different patients into 10 consecutive windows (each covering 10% of the seizure). In contradiction to the two previous studies, they found a steep increase in synchrony levels in the first and last windows during seizures (Kramer et al., 2010). However, they also found that seizures were characterized by networks with constant nodal degree and small-world topology, while the transition from ictal to post-ictal state was characterized by highly increased nodal degree and randomness. Further refining this strategy, Burns et al. used a data-driven approach to represent network dynamics with a finite set of representative networks. Their main result is that for some patients, there exists two states during which the SOZ is specifically disconnected (isolated focus state – IF) and overconnected (connected focus – CF), respectively. When present, the IF state occured at seizure initiation and lasted for about the first half of seizures. Importantly, patients for whom IF states could be detected had significantly better surgical outcome than patients for whom IF state was not detected (Burns et al., 2014). This important study shows that the epileptic zones

that specifically detach from the EN at seizure initiation are good candidates for surgical resection. Further refinement of the synchrony analyses reviewed here is possible by considering the directionality of connections through the assessment of effective connectivity.

Network dynamics: directionality. Formal distinction between contributions of outgoing and incoming connections in EN analysis was provided by Varotto et al. who compared the connectivity of intracranial electrode contacts in 10 patients with lesional epilepsy. They divided contacts into 3 groups: within the lesion (LES), involved in the seizure but outside the lesion (INV) and not involved in seizures (NINV) and showed that outgoing connections of LES and INV contacts increase significantly at seizure onset. Interestingly, while outgoing LES connections were directed towards the INV group, outgoing connections of the INV group were diffuse. In contrast, incoming connections did not show significant differences between the 3 groups (Varotto et al., 2012). In the same vein, it was shown that blind identification of the electrode contact with the highest number of outgoing connections at seizure initiation localized the surgically-defined SOZ in two patient series (8/8 - van Mierlo et al., 2013; 11/11 – (Wilke et al., 2010). Finally, there was also a good correlation between the percentage of connections exiting nodes localized within SOZ and percentage of seizure reduction after surgery (Wilke et al., 2010).

Network dynamics: the case of ICE. Since the early 2000s, our group started sampling insular regions with intracranial electrodes systematically when patients were suspected of either frontal, temporal, or parietal lobe epilepsy with inconsistent clinical semiology. We thus constituted a large database of ICE cases including icEEG recordings and recently started analysing network dynamics and topology. We found that most significant changes in

effective connectivity were found in the gamma band (Figure 7), more specifically at seizure initiation, electrographic shift and termination (Figure 8). In addition, insular contacts were characterized by an increase in outgoing connections at seizure initiation, followed by disconnection. These results are in agreement with those reported by Burns et al. (2014), which suggests that an IF state is present in patients with ICE. This interpretation is supported by the fact that most of our ICE cases were seizure-free after insulaectomy.

Conclusion

Insular cortex epilepsy is a challenging disease that can easily be mistaken for other forms of epilepsy for several reasons. First, clinical semiology is often confusing since the insula may generate a variety of symptoms classically associated with other types of focal epilepsy and because insular seizures can be asymptomatic until paroxysmal activity propagates to secondary brain structures. Second, standard clinical neuroimaging tests often fail to detect this type of epilepsy; no single non-invasive test is accurate enough to provide an efficient biomarker of insular cortex seizures or spikes. However, the most informative non-invasive tests are T1-contrast MRI imaging and sECD modelling of insular epileptic spikes, and consensus between MRI/MEG and any other test can reach the clinical threshold for proceeding with insulaectomy without recording icEEG.

Our current understanding of the functional networks involved in insular epilepsy is still mostly descriptive but ongoing efforts from our group and others have the potential to provide clinically useful information. Using MEG, we could establish functional connectivity-based signatures of two subtypes of insular cortex epilepsy and we are currently investigating the

potential of the signatures as biomarkers of ICE. In addition, investigating the causal relationships during seizures with icEEG, we found that the insula is necessary for initiating seizures but not for its maintenance. We are currently pursuing these investigations to relate the causal role of the insula during seizures with surgical outcomes following insulaectomy, with the aim to fine-tune the surgical approach and optimize its success.

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Figure captions

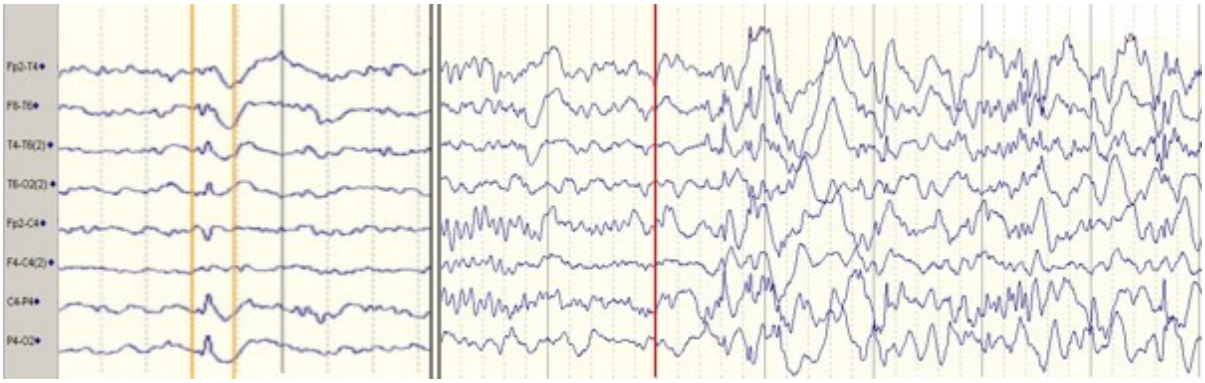


Figure 1. EEG recordings of the epileptic activity from the illustrative patient. The time axis (horizontal) is discontinuous as shown by the double vertical black lines. Interictal and ictal activity are displayed respectively to the left and right of the black lines. A clear temporo-central spike is displayed between the two vertical orange lines. A seizure starts right after the vertical red bar. From those traces, EEG does not allow the detection of the insular focus.

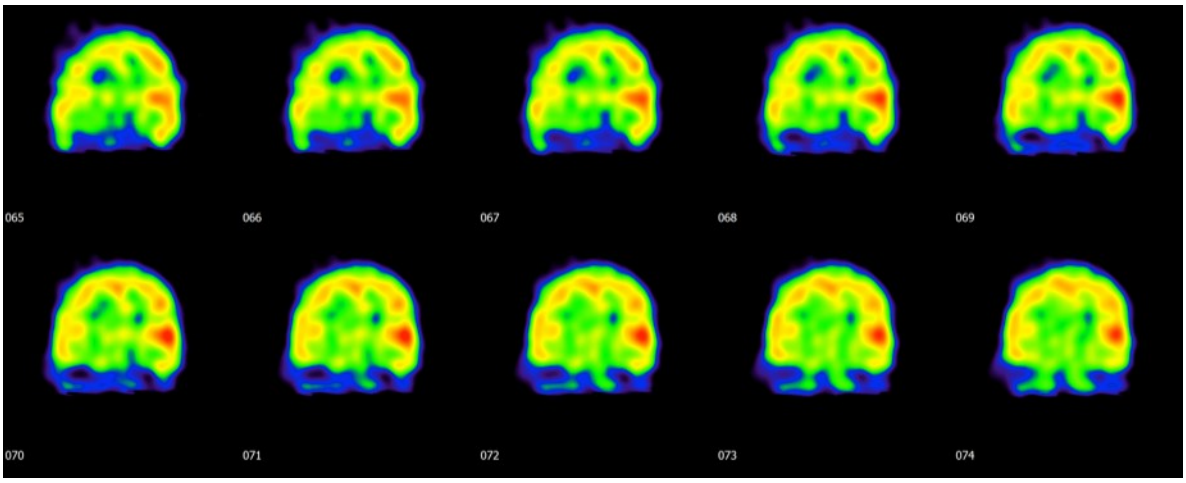


Figure 2. Ictal SPECT images from the illustrative patient. The selected coronal slices are displayed in the neurological convention (right hemisphere at the right) and span the antero-posterior axis of the insula. These slice show clear asymmetry in blood perfusion, the right insula showing clear hyper-perfusion as compared to the left side.

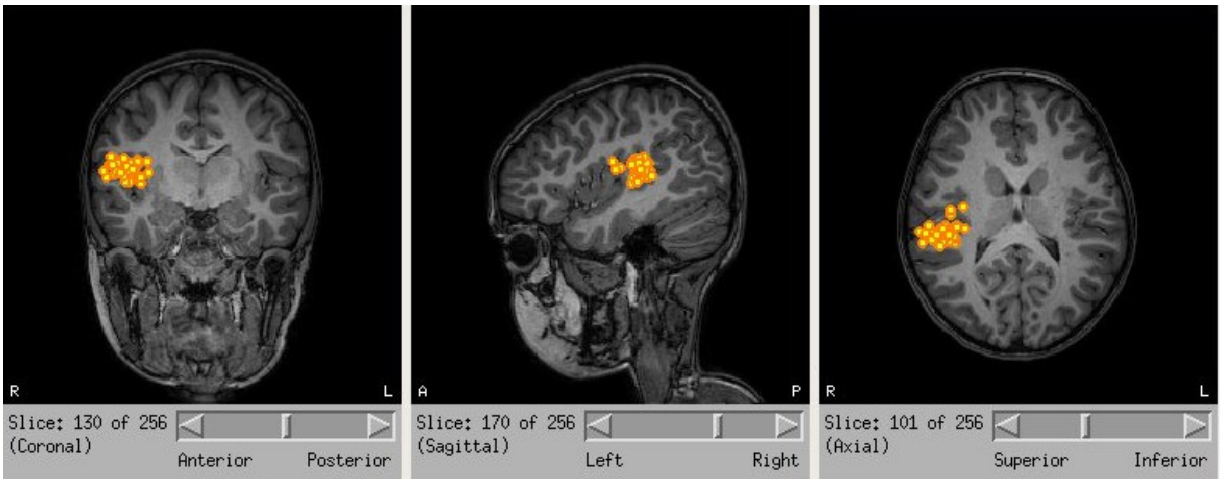


Figure 3. Single dipole modeling of the interictal spikes recorded from the illustrative patient using MEG, each dipole corresponding to a single spike. Localized dipoles clearly cluster in the posterior portion of the insula and in the centro-parietal opercula.

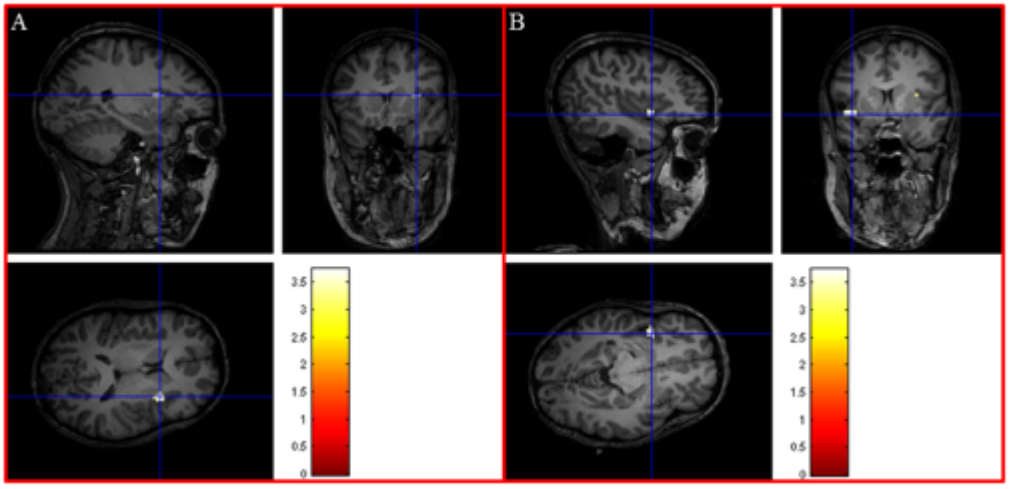
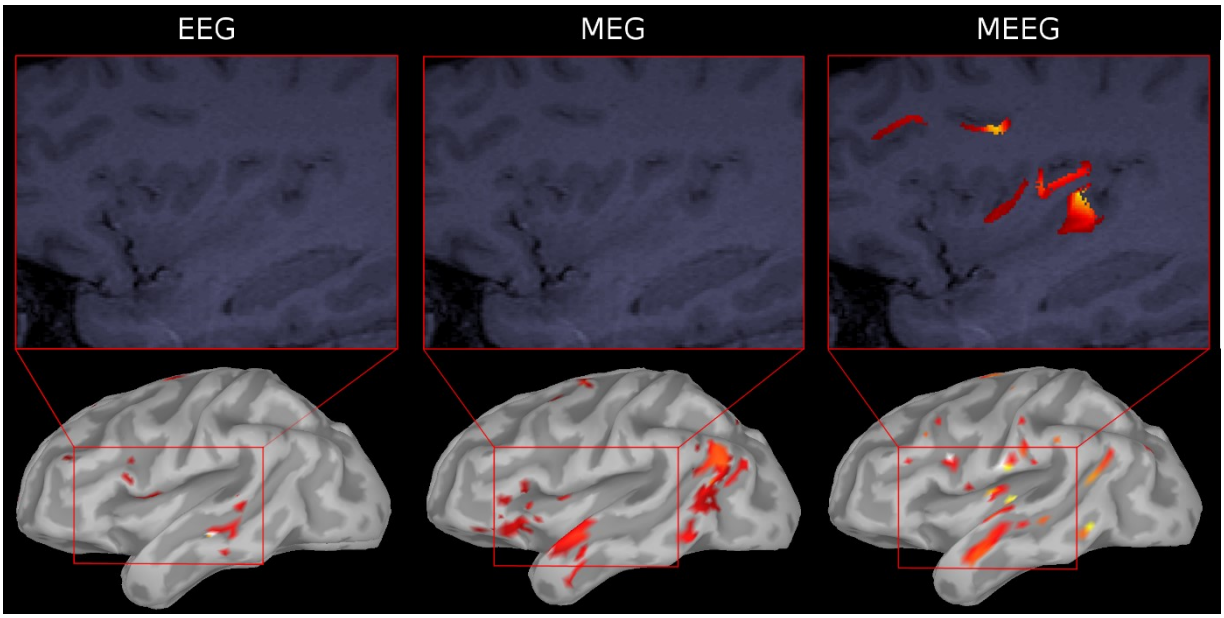
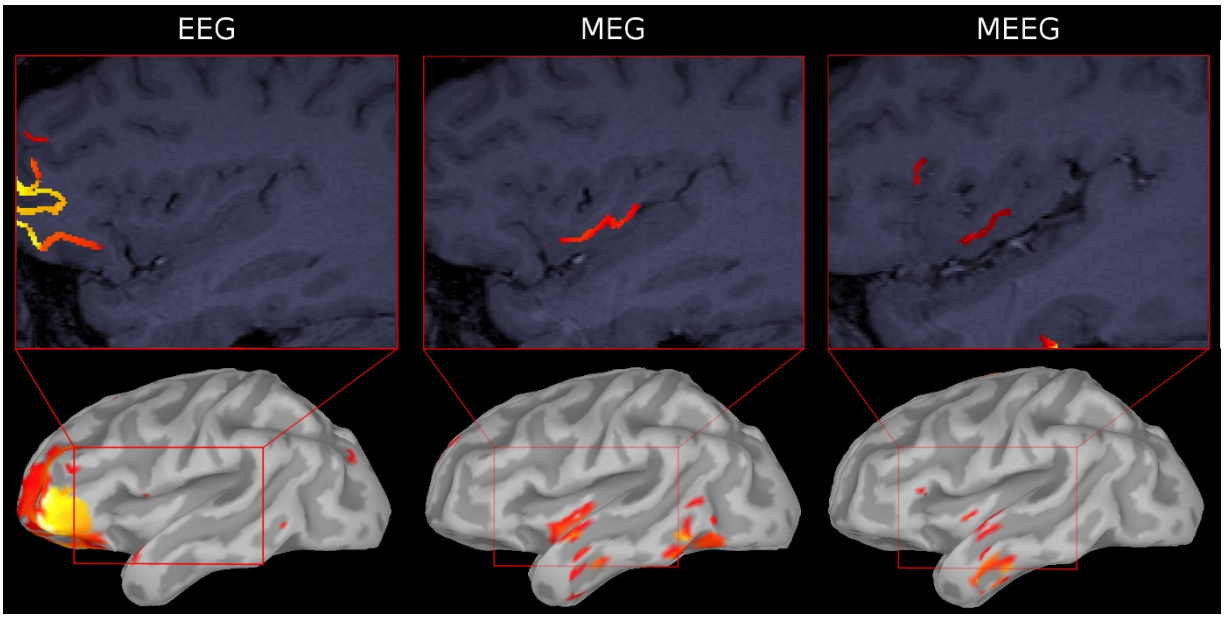


Figure 4. Combined EEG-fMRI recordings of interictal spikes from one patient of our cohort of insular cortex epilepsy. General linear model reveals a single BOLD activation cluster in the anterior dorsal portion of the insula. Although they were found in other patients, activation of other structures, such as overlying perisylvian cortex and the cingulate gyrus did not reach significance.



A



B

Figure 5a 5b. Combined EEG-MEG source reconstruction of 2 epileptic spikes from one patient with ICE. A) for this spike, the EEG was unable to detect the insular activation and reveals mainly activity in the orbitofrontal cortex. In turn, both MEG and MEEG could detect activation in the ventral region of the insula. B) for this spike neither EEG nor MEG could detect insular activation while MEEG clearly displays maxima of power in the ventral and posterior insular regions.

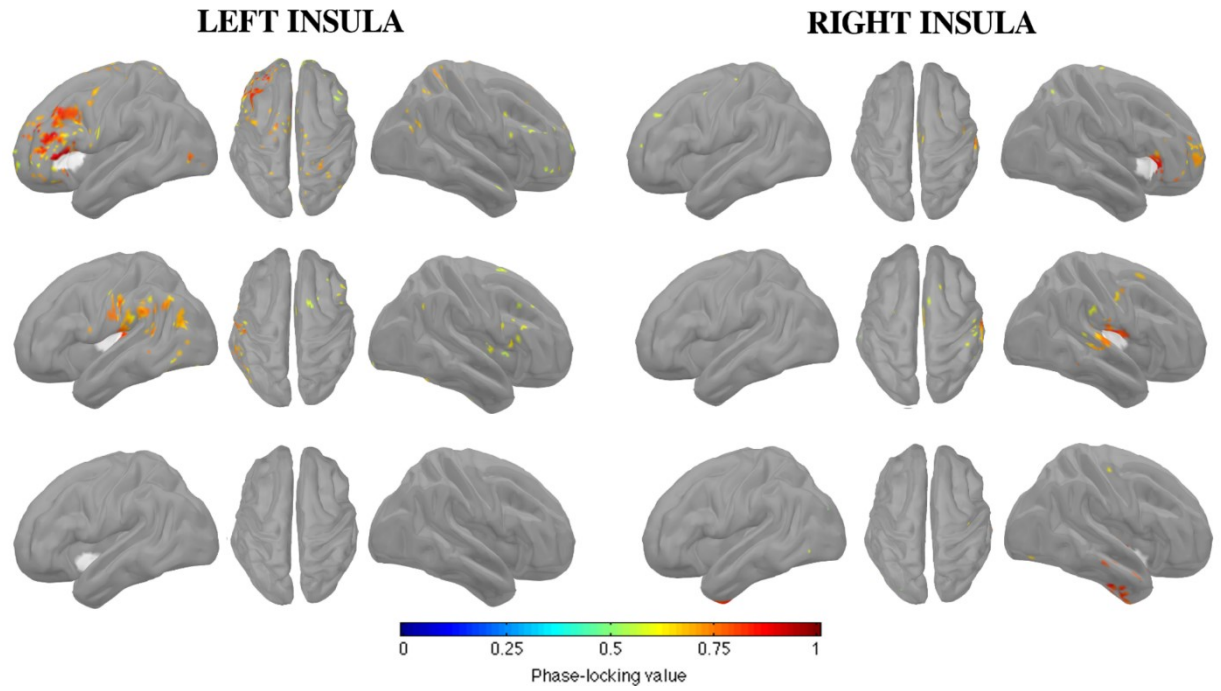


Figure 6. Functional connectivity of insular subregions during interictal spikes recorded with MEG and quantified using the phase-locking value of narrow-band filtered signal (beta band, 12-30Hz). Each insular subregion is represented in 3 panels (left, top and right views), with insular seeds appearing in white. Top row: anterior subregion; middle row: posterior subregion; bottom row: inferior subregion. The color scale encodes the strength of coupling insular seeds and the rest of the cortex, after statistical thresholding.

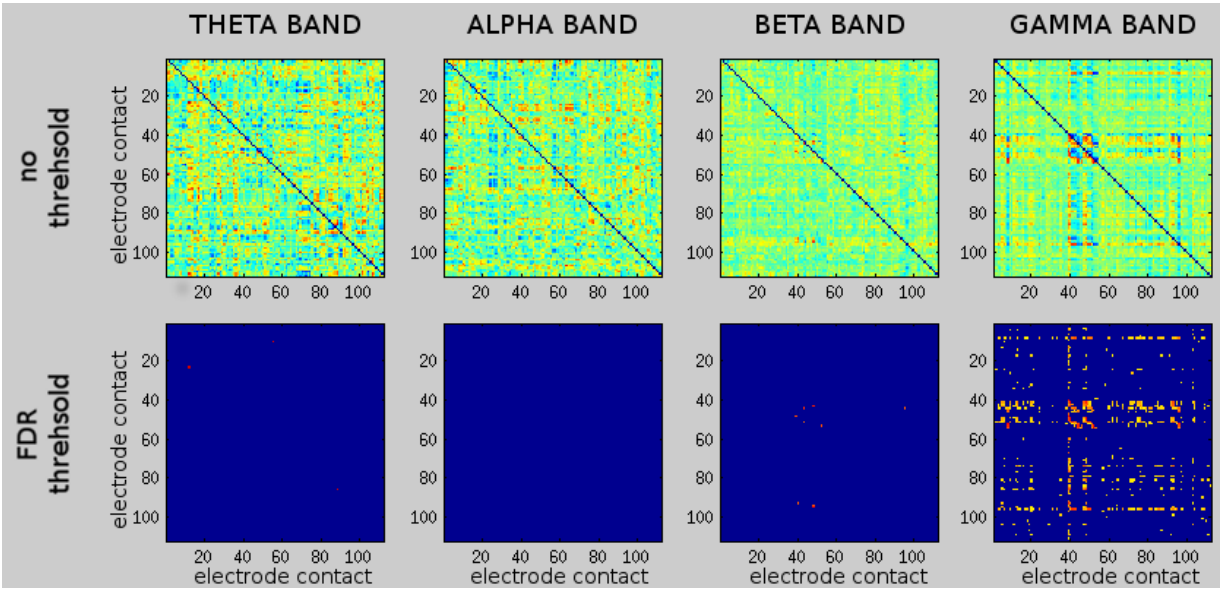


Figure 7. Effective connectivity at seizure onset computed from intracranial EEG data on 3 patients with insular cortex epilepsy. Effective connectivity is computed using the directed phase-lag index (Stam and van Straaten, 2012) in narrow-band filtered signals in the following frequencies: theta (4-7Hz), alpha (8-12Hz), beta (12-30Hz) and gamma (30-90Hz). Top row: raw connectivity matrices; bottom row: statistical threshold applied using the false-discovery rate technique. The null hypothesis was modeled using baseline data segments recorded 2 minutes before the beginning of seizures.

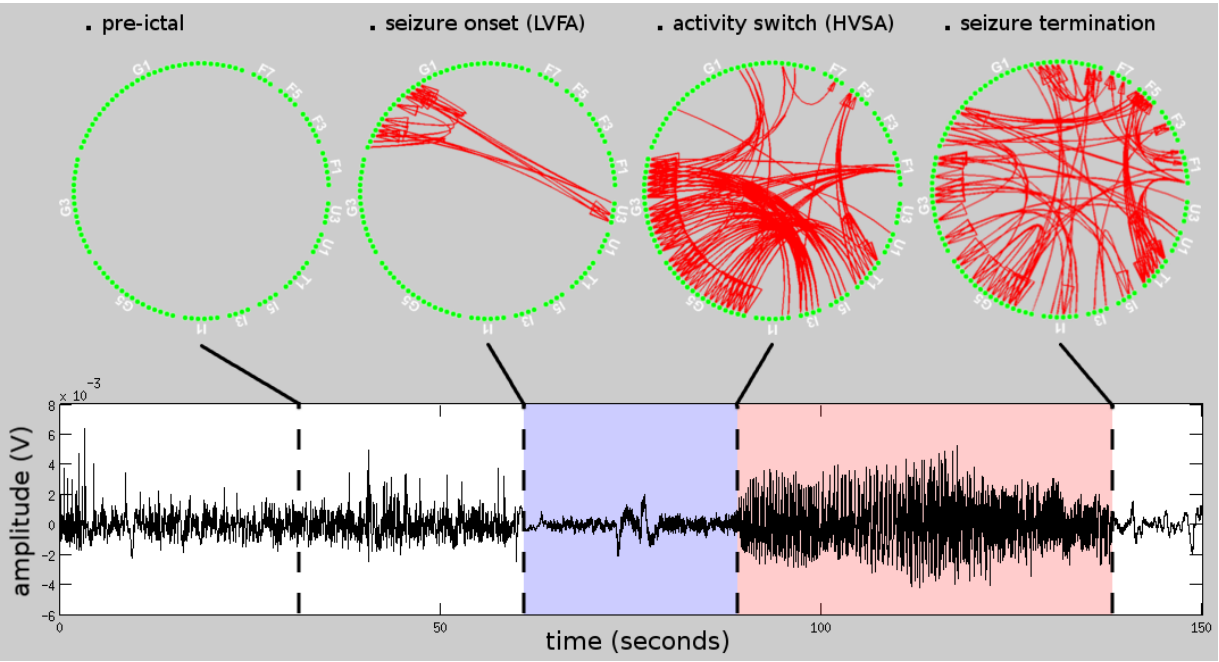


Figure 8. Network dynamics of insular cortex epilepsy. Thresholded connectivity matrices in the gamma band are displayed at transitions between brain states along seizures. At seizure initiation, the seizure onset zone (i.e. the insula – electrode U1, U3) is the main driving node of the epileptogenic network. At the transition from low-voltage fast activity to high amplitude slow oscillations, the insula detaches from the network and remains detached until seizure termination, which is marked by a dense and unstructured connectivity network.