Université de Montréal

La contribution de l'insula au traitement de l'information : Apports de l'EEG intracrânien et de l'évaluation comportementale

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La contribution de l'insula au traitement de l'information : Apports de l'EEG intracrânien et de l'évaluation comportementale

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Résumé

En raison de sa localisation en profondeur du cerveau, le rôle de l'insula dans le traitement de l'information est longtemps resté énigmatique. Or, l'avènement des techniques de stimulation électro-corticale et de neuroimagerie a permis de mettre en exergue son implication dans divers aspects du fonctionnement neuropsychologique. De plus en plus d'études suggèrent que le cortex insulaire joue un rôle clé dans le traitement des caractéristiques physiques des stimuli sensoriels, ainsi que dans le traitement de la saillance des informations. Les théories contemporaines avancent ainsi que l'insula serait une région cruciale dans le « réseau de saillance » et serait impliquée dans les processus sensoriels, émotionnels et attentionnels. Toutefois, la nature exacte de sa contribution demeure inconnue, notamment en raison des limitations intrinsèques des techniques d'investigation traditionnelles, ainsi que de la faible prévalence des lésions circonscrites à l'insula, d'autant que l'évidence clinique ne fait pas l'unanimité. En outre, les résections insulaires sont de plus en plus fréquentes chez les patients atteints d'épilepsie insulaire pharmaco-résistante. Cependant, les altérations neuropsychologiques d'une telle intervention restent mal connues. Ainsi, les études qui composent cette thèse visent à mieux comprendre la façon dont l'insula participe au traitement de l'information et les conséquences neuropsychologiques des résections insulaires sur les processus sensoriels, émotionnels et attentionnels.

Les deux premières études de cette thèse documentent les contributions respectives des portions antérieure et postérieure de l'insula au traitement attentionnel pour l'information sensorielle. Les réponses de l'insula lors de l'exécution de tâches attentionnelles de type *oddball* visuel et auditif sont enregistrées au moyen de l'EEG intracrânienne auprès de patients atteints d'épilepsie dont des électrodes ont été implantées dans l'insula dans le cadre d'une évaluation

préchirurgicale pour une épilepsie résistante à la médication. Les résultats suggèrent que l'insula antérieure participe au déploiement attentionnel volontaire aux alentours de 300-500 ms à la suite de la présentation de stimuli pertinents à la tâche en modalité visuelle et auditive, alors que la portion postérieure, quant à elle, est impliquée dans le traitement attentionnel automatique survenant de manière précoce, autour de 100 ms suivant la présentation d'informations auditives, indépendamment de la pertinence du stimulus. Les deux études suivantes qui composent cette thèse examinent les conséquences neuropsychologiques d'une résection au cortex insulaire sur le traitement sensoriel et affectivo-attentionnel, chez des patients épileptiques réfractaires à la médication qui ont subi une résection unilatérale de cette région. Leurs performances dans une tâche Dot-Probe révisée et dans un test de Stroop émotionnel, ainsi que leurs réponses à un questionnaire mesurant des patterns comportementaux sensoriels, sont comparées à celles d'un groupe de patients ayant subi une chirurgie d'épilepsie temporale et d'un groupe d'individus contrôles en santé. Les résultats mettent en évidence des altérations sensorielles et du contrôle des interférences émotionnelles à la suite d'une chirurgie d'épilepsie insulaire.

En somme, les données de cette thèse contribuent à une meilleure compréhension du rôle spécifique de l'insula au traitement de l'information sensorielle, saillante, émotionnelle et attentionnelle, au moyen de mesures neurophysiologiques et comportementales. Elles fournissent également un appui quant à la pertinence de développer des outils standardisés en évaluation neuropsychologique afin de mieux identifier les perturbations fonctionnelles associées à une épilepsie ou une chirurgie d'épilepsie insulaire.

Mots-clés : Insula, Réseau de saillance, Processus attentionnel, Émotions, Interférence, EEG intracrânienne, Épilepsie, Oddball, Dot-Probe, Stroop émotionnel.

Abstract

The role of the insular cortex in information processing has long been considered enigmatic, partly due to its deep location in the brain. However, the advent of direct electrocortical stimulation and neuroimaging approaches have shed light on its involvement in multiple of neuropsychological functions. An increasing number of studies suggest that the insular cortex plays a crucial role in processing the physical characteristics of sensory stimuli, as well as in the processing of salient information. Current theories argue that the insula would be a critical structure in the "salience network" and involved in sensory, emotional and attentional processes. However, the specific contribution of the insular cortex remains unknown, notably due to the intrinsic limitations of conventional approaches and the very low prevalence of lesions restricted to the insula, especially as little clinical evidence support these findings. Furthermore, although insular resections are becoming more frequent, the neuropsychological effects of this surgery remain unclear. Thus, the studies that make up this thesis aim to improve our understanding of the role played by the insula in the salient information processing and the neuropsychological consequences of the insular resections on sensory, emotional and attentional functions.

The first two studies of this thesis assess the respective contributions of the anterior and posterior insular portions in attentional processing towards salient and relevant sensory information. The insular responses during visual and auditory *oddball* attentional tasks are recorded by means of intracranial EEG (iEEG) in epileptic patients undergoing invasive iEEG, with electrode contacts implanted in the insula as part of a pre-surgical evaluation of their drug-resistant seizures. The results suggest that the anterior insula participates in voluntary attentional processing around 300-500 ms following the presentation of task-relevant stimuli in both visual and auditory modality, whereas the

posterior portion is involved in automatic processing occurring about 100 ms after auditory stimuli presentation, independent of task-relevant information. The next two studies examine the neuropsychological consequences of insular cortex resections on the sensory and affectivo-attentional processes, in drug-refractory epileptic patients who have undergone unilateral resection of this structure. Their performance in a revised Dot-Probe task and an emotional Stroop test, as well as their responses in a questionnaire assessing sensory behavioral patterns, were compared to a group of patients who had surgery for temporal lobe epilepsy and a group of healthy control. The results highlight alterations in sensory processing and emotional interference control following insular epilepsy surgery.

In sum, the neurophysiological and behavioral data in this thesis contribute to a better understanding of the specific role of the insula in the processing of sensory, salient, emotional and attentional information. Moreover, these findings highlight the need to further develop neuropsychological tests in order to better identify functional disturbances associated with insular epilepsy and insular resection surgery.

Keywords : Insula, Salience network, Attentional processing, Emotions, Interference, Intracranial EEG, Epilepsy, Oddball, Dot-Probe, Emotional Stroop.

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Liste des sigles et abréviations

Abréviations en français

EEG : Électroencéphalographie

ERP(s) : Potentiel(s) évoqué(s)

iEEG : Électroencéphalographie intracrânienne

IRM(f) : Imagerie par résonance magnétique (fonctionnelle)

MEG : Magnétoencéphalographie

Abréviation en anglais

AASP : Adolescent/Adult Sensory Profile

AD : Anxiety disorders

aI : anterior insula

BDI : Beck Depression Inventory

BOLD : Blood Oxygenation Level Dependent

CEN : Central-executive network

DMN : Default mode network

EEG : Electroencephalography

ERP(s) : Event-related potential

fMRI : Functional magnetic resonance imaging

GBR(s) : Gamma-band-responses

IASP : International Affective Picture System

iEEG : Intracranial EEG

ILE: Insular lobe epilepsy

IOR : Inhibition of return

ISI : Interstimulus interval

LIR : Large insular resection

LORETA : Low-resolution electromagnetic tomography

MMD : Major depressive disorders

pI : posterior insula

PIR : Partial insular resection

RT(s) : Reaction time(s)

STAI : State-Trait Anxiety Inventory

TLE : Temporal lobe epilepsy

À mes chers parents,

Avec toute ma reconnaissance.

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CHAPITRE I : INTRODUCTION

Introduction générale

L'insula, qui signifie en latin *île*, a été identifiée pour la première fois en 1809 par Johann Christian Reil qui lui donna le nom d'île de Reil (*Island of Reil*) en référence à sa forme. En raison de sa localisation en profondeur du cerveau, le rôle de l'insula est resté longtemps mystérieux. Ce n'est qu'au milieu du 20ème siècle avec l'avènement des techniques de stimulation corticale et de neuroimagerie que naît un intérêt pour l'étude du cortex insulaire dans le fonctionnement neuropsychologique et dans les conditions psychiatriques. Les travaux de ces dernières décennies menés sur l'insula ont mis en exergue son implication dans le réseau de saillance et dans une multitude de fonctions sensorielles et affectives. Or, le rôle spécifique de l'insula dans le fonctionnement neuropsychologique demeure encore imprécis, notamment, en raison de la faible prévalence des lésions circonscrites à l'insula et des limitations des techniques d'investigation traditionnelles. D'autre part, depuis l'apparition des techniques avancées en microchirurgie, la résection partielle ou radicale de l'insula est de plus en plus fréquente chez les patients souffrant d'épilepsie insulaire résistante à la médication. Toutefois, les séquelles neuropsychologiques d'une insulectomie restent mal connues. Or, la compréhension des altérations fonctionnelles rattachées à une ablation de l'insula s'avère nécessaire compte tenu du lien étroit entre les capacités du traitement de l'information et le bien-être des patients concernés. De plus, la mise en lumière d'altérations cognitives et émotionnelles subséquentes à une résection insulaire contribue à la compréhension des fonctions de l'insula dans le traitement de l'information.

1. Anatomie et connectivité de l'insula

1.1 Localisation

L'insula est considérée comme le cinquième et le plus petit lobe du cerveau, représentant approximativement entre 1 et 4 % de la surface corticale totale (1, 2). Cette structure majeure du système paralimbique, invisible en surface, est localisée en profondeur du cerveau à la base de la scissure de Sylvius, encastrée latéralement par les opercules des lobes frontal, temporal et pariétal, et médialement par le claustrum et la capsule interne, externe et extrême. Elle comporte les aires cyto-architectoniques 13 et 16 de Brodmann (3). Chaque hémisphère cérébral comporte une insula (4).

1.2 Plan macroscopique

L'insula se présente sous la forme d'une pyramide inversée à base triangulaire médialement et dont le sommet (c.-à-d. l'apex) se trouve proche du limen insulae. Elle est encerclée par le sillon appelé circulaire, comprenant les sillons péri-insulaires inférieur, supérieur, antérieur et postérieur, lesquels délimitent sa séparation avec les aires avoisinantes telles que les opercules frontal, temporal et pariétal (4-6). Sur le plan anatomique interne, l'insula est formée par un ensemble de gyri séparables en deux sous-régions insulaires par le sillon central de l'insula (c.-à-d. le sulcus central), nommées les portions (ou lobules) antérieure et postérieure. Le lobule antérieur comporte trois courtes circonvolutions (c.-à-d. gyrus court antérieur, moyen et postérieur) ayant en commun l'apex comme origine et distinguables selon l'ordre d'emplacement. Le lobule postérieur, quant à lui, contient deux longs gyri (c.-à-d. gyrus long antérieur et postérieur) positionnés obliquement et séparés par le sillon post-central. Quatre sillons intra-insulaires divisent ainsi le lobe insulaire en cinq

gyri (4). Bien que cela représente la structure anatomique commune de l'insula, il en demeure des variations interindividuelles et inter-hémisphériques (7).

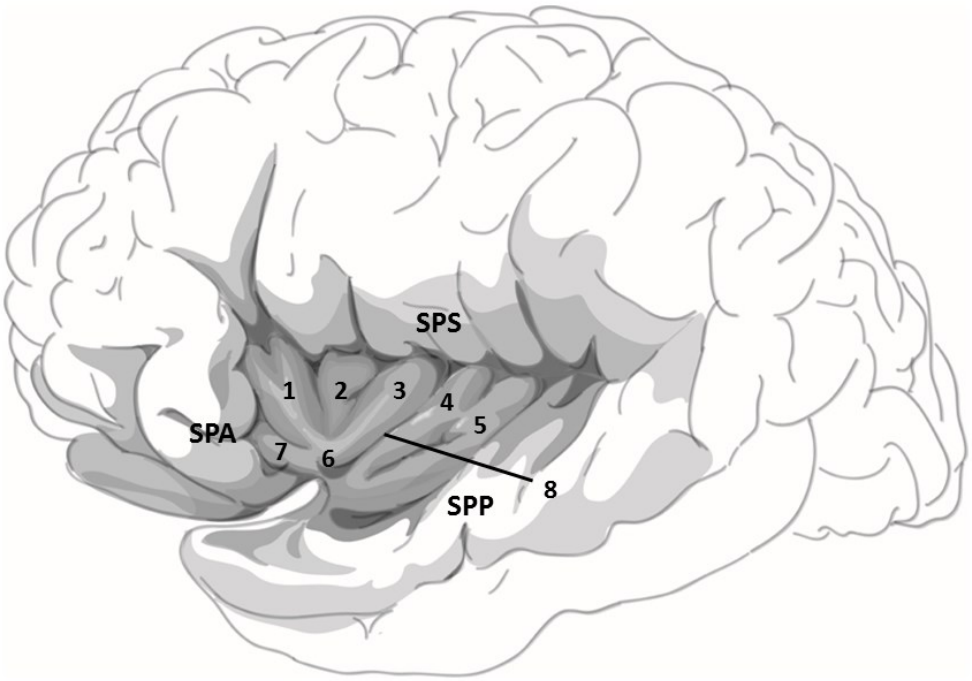

Figure 1. – Illustration du lobe insulaire et de ses principales subdivisions anatomiques : 1 : gyrus court antérieur ; 2 : gyrus court moyen ; 3 : gyrus court postérieur (gyrus précentral); 4 : gyrus long antérieur (gyrus post-central); 5 : gyrus long postérieur ; 6 : apex de l'insula ; 7 : gyrus accessoire ; 8 : sillon central de l'insula ; SPA : sillon péri-insulaire antérieur ; SPP : sillon péri-insulaire postérieur ; SPS : sillon péri-insulaire supérieur. Illustration de l'insula par Dr Tram Nguyen.

1.3 Histologie et vascularisation

Sur le plan cyto-architectural, le lobe insulaire est divisé en trois zones distinctes, basées sur des différences de forme, de nombre et de type des neurones des couches II et IV, et de lamination des couches en général (8, 9). Son organisation est circulaire et centrée autour de son pôle allocortical avec des zones fortement interconnectées le long des axes dorso-ventral et rostro-caudal. Plus

précisément, une zone agranulaire antéro-inférieure (péri-allocortex), caractérisée par la présence de neurones von Economo dans la couche V (10, 11) et contenant des neurones pyramidaux dans les couches II et IV, est entourée d'une zone dysgranulaire intermédiaire (pro-isocortex) s'étendant de la portion antérieure à la portion postérieure de l'insula et dans laquelle les couches II et IV sont difficilement distinguables. Enfin, une zone granulaire (isocortex) composée de cellules granulaires bien différentiables dans les couches II et IV couvre la portion postérieure dorsale de l'insula (12-15).

En outre, l'insula est vascularisée par une centaine de petites artères, dont la majorité prend son origine dans les segments M2 et M3 de l'artère cérébrale moyenne. Le drainage veineux de l'insula se fait principalement dans la veine cérébrale moyenne profonde pour sa portion postérieure et dans la veine cérébrale moyenne superficielle pour le gyrus court moyen. Les gyri courts antérieur et postérieur sont, quant à eux, des zones mixtes drainées alternativement dans la veine cérébrale moyenne profonde et superficielle (4, 6).

1.4 Connectivité

1.4.1 Connectivité structurelle chez les primates non-humains

Les premières recherches menées sur la connectivité de l'insula ont été effectuées auprès de singes rhésus sur lesquels des lésions insulaires étaient induites. À l'aide des techniques de dégénérescence neuronale et de traçage, ces études ont rapporté de riches connexions réciproques de l'insula avec plusieurs structures cérébrales corticales et sous-corticales, à travers les deux hémisphères. Ainsi, l'insula présentait de nombreuses connexions avec le lobe frontal (c.-à-d. opercule frontal, gyrus précentral, bulbe olfactif, aires pré-motrices et motrices, gyrus orbito-frontal et gyrus frontal inférieur), le lobe temporal (c.-à-d. opercule temporal, pôle temporal, cortex auditif primaire et associatif, gyri temporaux supérieur et inférieur, gyrus parahippocampal et cortex

entorhinal, périrhinal, et piriforme) et le lobe pariétal (c.-à-d. opercule pariétal et aires somato-sensorielles) (9, 16, 17). Des connexions avec des structures sous-corticales ont également été rapportées, incluant l'amygdale, le thalamus (dorsal, basal, et noyau lenticulaire), le nucleus accumbens, l'hypothalamus, l'hippocampe et le claustrum (9, 16-19).

1.4.2 Connectivité structurelle chez l'humain

Les connexions de l'insula avec les autres structures cérébrales ont été étudiées à l'aide de la tractographie. Cette technique utilise une méthode particulière du tenseur de diffusion avec l'imagerie par résonance magnétique et présente l'avantage de mettre en évidence les voies neuronales interconnectées (c.-à-d. les faisceaux neuronaux) dans le cerveau humain *in vivo*, bien que cette technique ne permette pas de différencier les connexions afférentes des efférentes (20). Plusieurs études ont révélé des connexions entre l'insula, en particulier sa portion antérieure ventrale et dorsale, et le lobe frontal, notamment avec le pôle frontal, le cortex orbito-frontal, les gyri frontaux supérieur, moyen et inférieur, dont l'aire de Broca dans sa partie postérieure, et l'opercule frontal. Avec le lobe temporal, l'insula présente des connexions avec l'opercule temporal, les gyri temporaux inférieur, moyen et supérieur (c.-à-d. le gyrus de Heschl). Plus précisément, la partie dorsale de l'insula antérieure et postérieure est connectée avec des faisceaux en provenance du gyrus de Heschl, du planum temporal et du gyrus temporal moyen, tandis que la partie insulaire ventrale est connectée avec les gyri temporaux inférieur et supérieur, le gyrus fusiforme temporal et le pôle temporal. Avec le lobe pariétal, sa partie dorsale antérieure et postérieure est connectée avec l'opercule pariétal, le précunéus, les gyri post-central (c.-à-d. aire somatosensorielle primaire), supramarginal et angulaire. Enfin, la portion postérieure de l'insula présente des connexions avec le gyrus fusiforme, le cortex occipital latéral et le pôle occipital (21-24). Des connexions avec des régions sous-corticales ont également été rapportées entre l'insula et l'amygdale, le thalamus, le gyrus cingulaire, l'hippocampe,

le putamen, le globus pallidus, le noyau caudé et le nucleus accumbens. Toutes ces connexions sont fortement symétriques entre les deux hémisphères. Enfin, des connections intra-insulaires permettant de véhiculer l'information entre les différentes portions de l'insula ont été suggérées (21, 22, 24, 25).

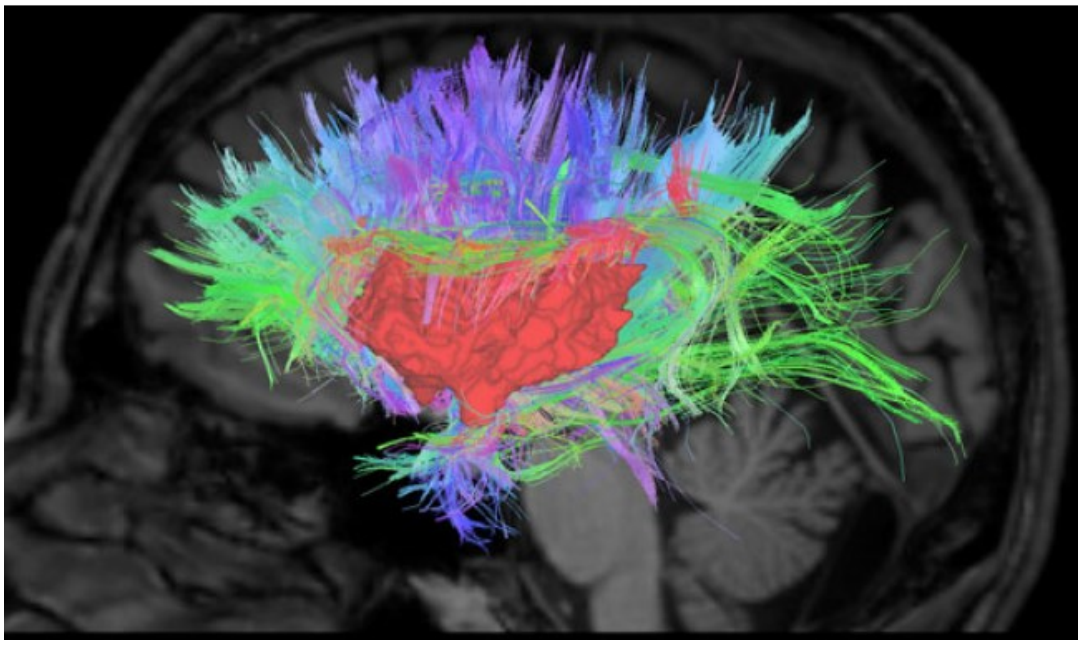

Figure 2. – Illustration des connexions corticales de l'insula d'un individu aléatoire à l'aide de la tractographie. Couleur : rouge : gauche-droite; vert : postérieur-antérieur; bleu : dorsal-ventral (23).

1.4.3 Connectivité fonctionnelle chez l'humain

La connectivité fonctionnelle à l'état de repos résulte de la mise en évidence de corrélations temporelles fortes entre les fluctuations spontanées du signal BOLD (*Blood Oxygenation Level Dependent*) de différentes régions cérébrales. Cette activité neuronale mesurée en imagerie par résonance magnétique fonctionnelle (IRMf) à l'état de repos traduit une activité physiologique

cérébrale intrinsèque, stable et à haute cohérence structurelle et fonctionnelle (26). Plusieurs études menées en IRMf à l'état de repos ont proposé une division de l'insula en trois sous-portions principales, basée sur des patterns de connectivité fonctionnelle. Une première portion intermédiaire-postérieure connectée aux aires pré-motrices (primaires, secondaires et supplémentaires), aux aires somatosensorielles (primaires et secondaires) et au cortex cingulaire postérieur, une seconde portion antéro-ventrale connectée principalement avec le sulcus temporal supérieur, l'amygdale et le cortex orbito-frontal, et enfin, une troisième portion antéro-dorsale connectée principalement avec le cortex cingulaire antérieur et le cortex préfrontal dorso-latéral (27-29). En ce qui concerne les connectivités fonctionnelles intra-insulaires, une étude en stimulation électrique intracérébrale menée auprès de patients atteints d'épilepsie réfractaire a révélé des connexions entre chaque gyrus insulaire, à l'exception des gyri courts antérieur et postérieur, et la majorité de ces connections étaient réciproques (30).

En raison de sa vaste connectivité à travers les structures corticales et sous corticales, il n'est pas surprenant que l'insula soit impliquée dans une multitude de fonctions regroupées en trois catégories principales, soit le traitement multisensoriel, affectif et cognitif. La section suivante aborde en détails ces fonctions.

2. Fonctions de l'insula

2.1 Division anatomo-fonctionnelle

L'insula est une région cérébrale impliquée dans un large éventail de fonctions, lesquelles sont appuyées par ses connections diverses avec de nombreuses structures corticales et sous-corticales. Il est de plus en plus établi dans la littérature scientifique que l'insula serait segmentée en quatre portions distinctes selon son organisation fonctionnelle, soulignée par une intégration caudo-rostrale de l'information (8, 31). En effet, la portion intermédiaire traiterait les stimuli chimio-sensoriels, alors que la région médio-postérieure les stimuli sensori-moteurs. La zone antéro-ventrale serait principalement impliquée dans les activités socio-affectives, tandis que la portion antéro-dorsale serait, quant à elle, recrutée lors de tâches cognitives requérant notamment la mémoire de travail et le langage. Ainsi, l'insula serait recrutée dans le traitement auditif, gustatif et olfactif (5, 32-35), ainsi que dans le contrôle somato-moteur (36). Elle serait également impliquée dans les fonctions autonomes, viscérales et vestibulaires (5, 37-39), de même que dans la perception de la douleur et de la température (40-42). Enfin, l'insula interviendrait dans des fonctions plus élaborées telles que l'intéroception (43), le traitement de la saillance (44) et des émotions (45), ainsi que dans les processus attentionnels (46).

L'évidence clinique appuie le rôle multimodal de cette structure cérébrale dans le fonctionnement neuropsychologique par la manifestation de déficits variables associés aux dommages insulaires. Les sous-sections suivantes visent à aborder les différentes fonctions dans lesquelles l'insula est impliquée, notamment son rôle dans le traitement sensoriel incluant l'audition, la vision et l'olfacto-gustation, dans le traitement vestibulaire et somato-moteur, ainsi que dans le traitement affectif et attentionnel.

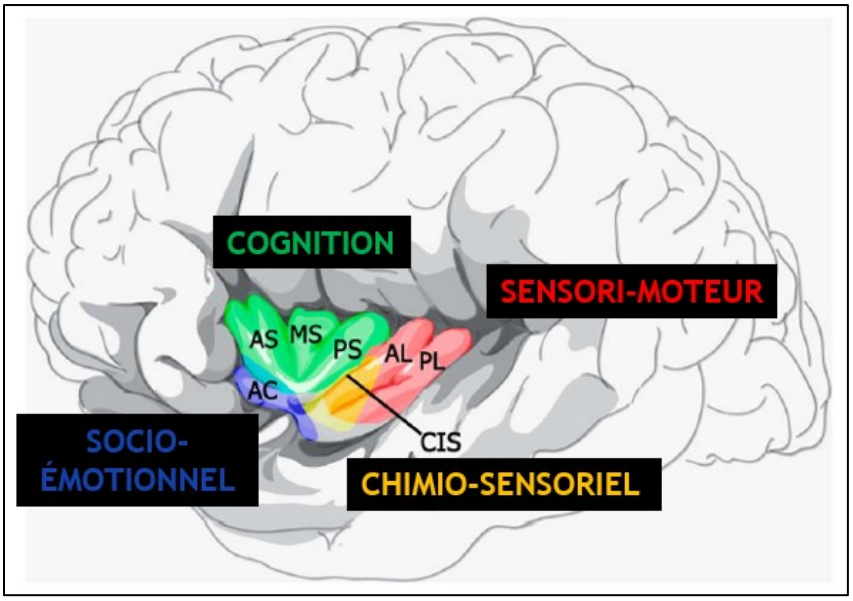

Figure 3. – Division anatomo-fonctionnelle de l'insula. Segmentation fonctionnelle en quatre portions distinctes : antéro-ventrale : socio-émotionnel; antéro-dorsale : cognition; intermédiaire : chimio-sensoriel; médio-postérieure : sensori-moteur. Figure modifiée de sa publication d'origine (47).

2.2 Traitement multi-sensoriel

2.2.1 Processus auditif

Des travaux en études de lésion ont rapporté un large éventail de plaintes auditives rattachées à un dommage de l'insula. Une étude de cas auprès d'un rare patient avec une lésion insulaire bilatérale a documenté des difficultés pour le traitement de sons non-verbaux, une anhédonie musicale et des déficits dans la reconnaissance des voix familières (48). Une autre étude de cas, menée chez un patient avec lésion vasculaire impliquant l'insula droite et touchant la matière blanche adjacente, a rapporté des déficits dans l'identification des sons verbaux présentés à l'oreille gauche (49). Une dernière étude de cas de Griffiths et de ses collaborateurs (50) a souligné une difficulté majeure pour le ressenti musical suite à une lésion insulaire gauche s'étalant aux régions frontales et

amygdaliennes gauches. Une étude menée auprès de huit patients avec lésion insulaire unilatérale a conclu que l'insula serait impliquée dans le traitement fin de stimuli auditifs, tels que le traitement temporel et séquentiel des sons (51). Plus récemment, trois cas d'hyperacousie suivant une lésion insulaire unilatérale ont été rapportés. Cette hyperacousie se traduisait par une diminution du seuil d'inconfort face à l'intensité de stimuli auditifs présentés aux deux oreilles séparément. Dans deux des cas sur trois, l'hyperacousie était plus prononcée du côté ipsilatéral à la lésion. Les patientes atteintes présentaient aussi des difficultés aux tâches de reconnaissance de fréquences et de durées de sons (33).

Les techniques d'investigation en neuroimagerie permettent de s'affranchir de certaines limitations des études de lésion incluant notamment l'hétérogénéité des structures adjacentes lésées qui rend difficile l'énumération des déficits fonctionnels spécifiquement liés au dommage insulaire. Ainsi, une première étude en tomographie par émission de positrons avait rapporté une activation de l'insula antérieure lors d'une tâche d'écoute passive de sons (52). Plusieurs autres travaux en IRMf ont par la suite documenté une activation de l'insula lors de tâches auditives de type *oddball* pour la détection de stimuli cibles et nouveaux, avec une plus forte réponse pour les cibles, ainsi que lors de tâches de détection spatiale et temporelle de sons (32, 53-55).

Des études de stimulation électro-corticale profonde, menées auprès de patients épileptiques implantés dans le cadre d'une évaluation pré-chirurgicale pour une épilepsie pharmaco-résistante, ont documenté des perturbations auditives en réponse à des stimulations dans la région postérieure de l'insula principalement, telles que des hallucinations auditives, la sensation d'écho auditif, des sifflements et des bourdonnements, soutenant ainsi l'implication de l'insula dans le traitement auditif (5, 38, 56-58).

2.2.2 Processus visuel

L'implication de l'insula dans le traitement visuel est bien moins consistante que dans l'audition. Des études en neuroimagerie ont rapporté une activation de l'insula lors de tâches de discriminations fines, de déplacements et de reconnaissances de stimuli visuels (59-61). Pessoa et ses collaborateurs (62) ont également mis en évidence le rôle crucial de l'insula antérieure dans la reconnaissance des expressions faciales émotionnelles, au même titre que l'aire fusiforme des visages. Il faudrait toutefois considérer que les implications précédemment citées peuvent en outre s'expliquer par les ressources attentionnelles déployées pour traiter les stimuli saillants et émotionnels, rendant le rôle spécifique de l'insula dans le traitement visuel incertain.

2.2.3 Processus olfacto-gustatif

Bien que rarement rapportées, des perturbations olfacto-gustatives peuvent se manifester suivant un dommage insulaire. Mak et ses collaborateurs (34) ont rapporté une augmentation de l'intensité perçue pour les goûts fortement plaisants et déplaisants ainsi qu'envers les odeurs déplaisantes présentés controlatéralement à une lésion insulaire, alors que d'autres études ont documenté une diminution de l'intensité perçue pour les goûts présentés ipsilatéralement à la lésion uniquement (63), ou encore une perte de la sensation de faim, un défaut dans la reconnaissance du goût et des intensités, une diminution du plaisir gustatif et une sensation de goût désagréable persistant dans la bouche (64-68). Les séquelles insulaires de ces cas cliniques pouvaient concerner la portion antérieure ou postérieure, l'hémisphère gauche ou droit, ainsi que des lésions dans les structures adjacentes.

Les données obtenues à l'aide de l'IRMf ont permis d'objectiver l'implication de l'insula dans le traitement olfacto-gustatif à travers une activation conjointe de l'insula lors de la présentation de

stimuli olfacto-gustatifs avec les structures principales du système olfacto-gustatif, telles que le cortex piriforme, le tubercule olfactif, l'amygdale, le cortex orbito-frontal et les opercules fronto-pariétal (35, 69). En particulier, l'insula antérieure serait impliquée dans la discrimination des odeurs et des goûts en termes de valence, alors que sa portion intermédiaire répondrait préférentiellement à l'intensité (70, 71). D'autre part, ces observations sont appuyées par des études de stimulation électro-corticale de l'insula, lesquelles ont rapporté des réponses gustatives telles qu'une sensation de goût métallique dans la bouche (58, 72).

2.2.4 Processus vestibulaire

L'implication de la région pariéto-operculo-insulaire dans le traitement vestibulaire est appuyée par plusieurs études de stimulation corticale lesquelles ont rapporté des réponses vestibulaires (c.-à-d. vertiges et déséquilibre) lors de la stimulation de l'insula postérieure principalement (38, 42, 56, 57). De manière concordante, des méta-analyses d'études en neuroimagerie ont identifié l'insula postérieure, l'opercule pariétal et la région rétro-insulaire comme les structures clés dans le système vestibulaire (73, 74). Frank et ses collaborateurs (75) ont également souligné le rôle de l'insula dans l'intégration des stimuli visuels et de la sensation du mouvement pour la perception du *self-motion*. Toutefois, l'évidence clinique ne fait pas l'unanimité concernant le rôle crucial de l'insula dans le traitement vestibulaire (76). En effet, une seule étude de cas a rapporté des symptômes vestibulaires à la suite d'un dommage dans l'insula antérieure (77).

2.2.5 Processus viscéro-somato-moteur

Les premiers travaux de stimulation électro-corticale directe de l'insula ont mis en évidence des réponses viscérales incitant la communauté scientifique à surnommer l'insula le « cerveau viscéral » (78). D'autres études ont par la suite confirmé son rôle central dans le traitement viscéral,

ainsi que dans le traitement somato-moteur, par des réponses viscérales (c.-à-d. nausées), motrices (c.-à-d. élévation du bras) et somato-sensorielles (c.-à-d. sensation de chaleur, picotements et engourdissements) suivant une stimulation de l'insula (5, 38, 39, 56-58, 72, 79). D'autres études ont également suggéré un rôle de l'insula postérieure dans le toucher discriminatif (80, 81). Par la suite, il a été proposé que l'insula joue un rôle plus élaboré dans l'intéroception, soit dans la perception des changements physiologiques du corps et des sensations internes (37). Suivant une intégration caudo-rostrale, les signaux intéroceptifs sont en premier lieu acheminés dans sa portion postérieure, puis intégrés ensuite dans les portions intermédiaire et antérieure où l'homéostasie des états physiologiques de l'organisme est construite, à travers la sensation de soif, la conscience du rythme cardiaque, les distorsions viscérales, le sentiment subjectif et la représentation du « moi matériel ». Ainsi, l'insula pourrait être considérée comme le corrélat neuronal de la conscience de soi (37, 43, 82, 83).

2.2.6 Synthèse I

En somme, l'ensemble des études rapportées dans les sous-sections précédentes semble compatible avec une caractérisation de l'insula comme un « site de convergence multimodal » dans lequel les informations de divers systèmes fonctionnels sont acheminées, incluant les informations sensorielles auditives, visuelles et olfacto-gustatives, l'information vestibulaire et sensori-motrice, ainsi que les sensations viscérales. Sur le plan clinique, toutefois, les données ne sont pas toutes concordantes, cela étant explicable notamment par la faible incidence des lésions insulaires focales, par les dommages insulaires hétérogènes (c.-à-d. portions et hémisphères), ainsi que par les diverses structures avoisinantes lésées. De plus, les modalités multi-sensorielles sont usuellement mesurées séparément et sur un très faible échantillon. Ainsi, plusieurs interrogations demeurent quant à l'implication cruciale et spécifique de l'insula dans le traitement multisensoriel, en particulier dans les

différents patterns comportementaux sensoriels tels que la sensibilité, l'enregistrement et la recherche sensorielle.

2.3 Traitement de l'information affective

2.3.1 Expérience émotionnelle

A la fin du 19e siècle, la théorie de l'émotion de James-Lange, classiquement classifiée comme la position « périphéraliste » des émotions, prône l'idée que la cause du déclenchement d'une émotion est liée à la perception des changements périphériques induits par l'événement émotionnel. Cette position théorique de l'émotion affirme que les émotions sont générées par les états du corps et que la perception de la rétroaction corporelle mène au sentiment subjectif, qui est l'émotion. Ainsi, les réponses physiologiques précèderaient la conscience émotionnelle (84, 85). Par opposition, la théorie dite « centraliste » de Cannon et Bard suggère que les réponses corporelles sont le résultat, et non la cause, de l'expérience émotionnelle (86-88). Bien qu'aujourd'hui controversé, le rôle causal des changements corporels dans l'émergence de l'émotion reste une proposition défendue par certaines théories contemporaines (89-91), dont la théorie des marqueurs somatiques de Damasio (92).

Usuellement, le sentiment subjectif se définit comme l'expérience consciente de nos émotions qui survient durant un traitement supraliminal de stimuli ou d'événements affectifs (93). L'insula a été singularisée comme le substrat neuronal de la genèse de l'expérience émotionnelle subjective par l'intégration des signaux du milieu viscéral vers une représentation intéroceptive des états du corps (37, 82, 91, 94, 95). Des données obtenues à l'aide de l'IRMf ont d'ailleurs objectivé l'interaction entre la sensibilité aux indices intéroceptifs, l'expérience émotionnelle négative vécue et l'activation de l'insula antérieure, à travers des corrélations positives (96). De plus, la conscience

émotionnelle permettrait d'émettre la meilleure réponse comportementale et motivationnelle face à une situation émotionnellement éprouvante (97, 98). Les données cliniques sont d'ailleurs en accordance avec le rôle prépondérant de l'insula dans la conscience émotionnelle par son rôle dans le trouble de l'alexithymie, lequel se caractérise par une difficulté à identifier, différencier et exprimer ses émotions (99).

2.3.2 'Appraisal' émotionnel

D'après l'approche cognitive componentielle de plusieurs théories contemporaines de l'émotion, le traitement de l'information émotionnelle se caractérise par une évaluation séquentielle du stimulus ou de l'événement affectif en fonction, en outre, de sa pertinence, son niveau d'*arousal*, sa valence, son implication, sa significativité et le potentiel de maitrise qui lui est assigné, influençant les réponses physiologiques, motivationnelles, cognitives, expressives ainsi que le sentiment subjectif (100-105). Ce processus permet de mobiliser de façon optimale les ressources de l'organisme et de maintenir l'homéostasie (106-108). L'insula, à travers ses connexions réciproques avec l'amygdale, le cortex cingulaire, le cortex orbito-frontal, l'hypothalamus et les ganglions de la base, est de plus en plus désignée comme un centre cortical impliqué dans l'évaluation des stimuli affectifs (27, 94, 109).

De manière récurrente, la recherche en neuroimagerie a objectivé la place de l'insula dans le processus émotionnel par son activation lors de rappels d'événements personnels de joie, de peur, de tristesse et de colère, ainsi que lors de présentations et de reconnaissances de stimuli visuels et auditifs à caractère émotionnel (94, 110-112). En outre, plusieurs études de cas menées auprès de patients souffrant de lésions de l'insula et de régions adjacentes ont rapporté une altération sélective pour la reconnaissance et la discrimination des expressions faciales de dégoût (113-117). Cependant, une série de cas récente a mis en évidence des altérations dans la reconnaissance des expressions faciales de peur, de joie et de surprise suivant une résection partielle ou complète du cortex insulaire

pour le contrôle de crise épileptique, révoquant ainsi sa limitation au traitement sélectif du dégoût (118). D'autres études de lésion ont également appuyé cette assertion (119-121), ainsi qu'une méta-analyse d'études en neuroimagerie (112).

Les données cliniques plaideraient en outre pour une contribution de l'insula pour l'évaluation émotionnelle à travers l'attribution de la valence et du niveau d'*arousal* (c.-à-d. excitabilité émotionnelle) pour l'information affective. À la suite d'une lésion insulaire unilatérale, Berntson et ses collaborateurs (122) ont en effet rapporté des perturbations dans l'évaluation de l'*arousal* et de la valence d'images émotionnelles, lesquelles se traduisaient par une tendance à attribuer une valeur neutre aux images plaisantes et déplaisantes, ainsi qu'une intensité moindre. Des travaux en neuroimagerie menés auprès de sujets sains ont toutefois nuancé ces observations cliniques en suggérant que l'implication de l'insula dans le traitement des émotions dépendrait du degré d'excitabilité du contenu émotionnel plutôt que de sa valence. Ainsi, une image de valence très positive ou très négative avec un fort niveau d'*arousal* produisait une réponse de l'insula antérieure, alors que pour une image faiblement chargée émotionnellement, son activation était moindre (111, 123). Le lien fréquemment observé entre l'émotion du dégoût et l'insula pourrait d'ailleurs s'expliquer par la forte excitabilité émotionnelle induite par cette émotion comparativement aux autres (124). Enfin, d'autres auteurs ont mis en évidence que la reconnaissance du niveau d'*arousal* d'un stimulus ou d'un événement émotionnel implique la conscience intéroceptive sous-tendue par les états internes émotionnels, laquelle est régulée par l'insula (36, 45).

2.3.3 Synthèse II

Il est de plus en plus établi que le cortex insulaire serait impliqué dans le traitement de l'information affective. Outre son implication dans la conscience émotionnelle subjective liée à la représentation interne des états affectifs, l'insula serait associée aux traitements évaluatifs des

émotions négatives et plus particulièrement au dégoût. Toutefois, d'autres travaux défendent davantage un rôle dans l'évaluation de l'*arousal* émotionnel plutôt que de la valence. Ainsi, la nature exacte de la contribution spécifique de l'insula au traitement affectif demeure imprécise, rendant difficile l'énumération des perturbations émotionnelles liées à un dommage insulaire focal.

2.4 Traitement attentionnel

2.4.1 Principe général

Le traitement attentionnel se réfère à un ensemble de sous-processus de bas et de haut niveau cognitif qui permet d'harmoniser la relation entre la pensée et l'action tout en favorisant les processus de planification et de prise de décision (125). L'attention sélective, plus spécifiquement, permet une focalisation de nos ressources sensorielles et cognitives sur un stimulus au détriment d'autres jugés moins pertinents (126). L'orientation attentionnelle est communément introduite par deux processus dichotomiques nommés *endogène* et *exogène*. Le premier renvoie à la dimension intentionnelle du traitement attentionnel, régi par un mécanisme dit *top-down* ou descendant de haut niveau, opéré par le déploiement de ressources attentionnelles volontaires. Le second, quant à lui, traduit un traitement attentionnel sensoriel perceptif, automatique et involontaire sous-tendu par un mécanisme dit *bottom-up* ou ascendant de bas niveau, motivé par les caractéristiques saillantes des informations (127-129). De plus, la flexibilité et l'adaptation du comportement reposent sur des fonctions exécutives telles que l'inhibition d'une réponse prépondérante (c.-à-d. saillante à caractère exogène) et la sélection entre des alternatives de réponses (c.-à-d. pertinentes à caractère endogène). La notion d'inhibition se définit comme la capacité à supprimer une réponse inappropriée, naturelle ou automatique et à éviter les interférences, guidant les ressources attentionnelles vers un déploiement d'engagement ou de désengagement (126, 127, 130, 131). Les soubassements

neuronaux impliqués sont le cortex préfrontal dorso-latéral, le gyrus frontal inférieur, le cortex pariétal postérieur, le cortex cingulaire antérieur et l'insula antérieure (125, 132).

2.4.2 Méthodes d'investigation

2.4.2.1 Enregistrement en potentiel évoqué

Le potentiel évoqué est défini comme une modification de l'activité électrique produite par le système nerveux central en réponse à une stimulation externe (visuelle, auditive, chimio-sensorielle ou tactile) ou interne (cognitive), enregistrée au moyen de l'électroencéphalographie (EEG) (de surface et intracrânienne) et de la magnétoencéphalographie (MEG). Bien que le terme *potentiel évoqué* (ERP) soit utilisé pour tout type de changement du potentiel électrique, certains auteurs font parfois une distinction entre les potentiels liés à des événements endogènes (c.-à-d. *Event-Related Potential* en anglais) de ceux dits exogènes (c.-à-d. *Evoked-Potential* en anglais). Ils se visualisent par des séquences de déviations négatives et positives, appelées déflections, pics, ondes ou composantes, distinguables selon leurs latences et leurs amplitudes (132-134). Ces déflections sont utilisées comme marqueurs neurophysiologiques des différentes étapes du traitement de l'information, allant d'un traitement des caractéristiques physiques élémentaires aux étapes plus avancées impliquant des processus mentaux élaborés (134).

Les processus attentionnels sont associés à plusieurs déflections, dont la N1 et la P3 traduisant des traitements attentionnels distincts. La défection *N1* (ou *N100*) est une onde d'amplitude négative indexée à une latence de 100 ms (± 50) suivant la présentation de stimuli auditifs indépendamment de la pertinence, saillance et familiarité. Elle reflète un niveau de vigilance appelé passif envers les propriétés physiques des stimuli sensoriels en faisant recours à un mécanisme *bottom-up* (135, 136). Les sources neuronales de la genèse de la N1 se situent dans le sillon temporal supérieur, le cortex

temporo-pariétal, le cortex auditif et la zone fronto-centrale (137-139). La déflection *P3* (ou *P300*) est, quant à elle, une onde d'amplitude positive indexée aux alentours de 250 – 500 ms après la présentation de stimuli multimodaux (140-145). Elle se divise en deux composantes nommées *P3a* et *P3b*. La composante P3a est amorcée lors de la présentation de stimuli nouveaux, saillants et inattendus. Il s'agit d'un traitement pré-automatique, souvent qualifié de pré-attentionnel. La composante P3b reflète, quant à elle, un traitement attentionnel volontaire dirigé vers un stimulus cible sous-tendu par un mécanisme *top-down* (146). Au moyen d'un paradigme *oddball* auditif, l'étude de Mulert et de ses collaborateurs (147) menée par enregistrement en EEG avec localisation de sources a documenté un indexage de la composante P3a vers 300 ms suivant la présentation d'un son cible généré dans la région frontale, alors que la P3b était évaluée 30 ms après la P3a en région pariétale. Ainsi, la composante P3a reflèterait un traitement de déviation du foyer attentionnel à mi-chemin entre les mécanismes *bottom-up* et *top-down* tandis que la P3b traduirait la mise à jour en mémoire de travail lorsqu'un stimulus est volontairement détecté et traité (148-150).

2.4.2.2 Analyse en temps-fréquence

L'activité oscillatoire du cerveau, représentée par plusieurs rythmes fréquentiels à travers le temps, apporte une contribution additionnelle aux potentiels évoqués dans la caractérisation des processus sous-jacents de l'attention (151, 152). L'analyse de ces oscillations permet une décomposition du signal électrique en fréquences oscillatoires à travers le temps dont l'axe horizontal représente le temps et l'axe vertical les fréquences. Les différents rythmes oscillatoires tels que les fréquences gamma, alpha et thêta sont associées à des traitements attentionnels distincts et facilement différenciables par le support temporel, lequel est étroit pour les fréquences basses tandis que large pour les fréquences hautes (153, 154).

Plusieurs travaux menés en EEG de surface et en intracrânien ont rapporté la présence d'oscillations dans la bande de fréquence gamma (30-150 Hz) lors de traitements sensoriels et attentionnels (155-158). A l'aide de tâches attentionnelles de type *oddball*, certains auteurs ont mis en évidence un pic d'activité oscillatoire autour de 40 Hz à environ 30 ms suivant la présentation de stimuli familiers et déviants alors qu'un second pic vers 350 ms n'était observé que pour les stimuli pertinents à la tâche (159, 160). Ces observations supportent ainsi la présence de fréquence oscillatoire gamma dans le traitement attentionnel de bas et de haut niveau. D'ailleurs, la manifestation de cette fréquence serait liée à la genèse des ondes N1 et P3 (157, 161). De manière semblable à la fréquence gamma, la réponse oscillatoire thêta (4-7 Hz) est mesurée dans des tâches d'attention avec des pics d'activité à 150 ms suivant la présentation de stimuli auditifs non-spécifiques et à 250 ms pour les stimuli pertinents (162-166). Canolty et ses collaborateurs (167) ont d'ailleurs rapporté que la fréquence haut gamma serait verrouillée en phase avec les oscillations thêta. Pour finir, la fréquence alpha (8-12 Hz) traduit un mécanisme de suppression attentionnel envers les informations non-pertinentes à la tâche, lequel est souligné par la présence d'oscillations alpha dans les régions cérébrales qui ne sont pas impliquées dans l'exécution de la tâche, alors qu'une absence est observée dans les régions recrutées (168-171).

2.4.3 Réseau de saillance

La saillance d'un événement, d'un objet ou d'une sensation se définit par sa singularité à déclencher l'allocation de ressources attentionnelles selon un seuil déterminé (172). Avec le cortex cingulaire antérieur, le cortex préfrontal et l'opercule frontal, l'insula antérieure constitue une structure majeure du réseau de saillance par son rôle dans la détection des informations ascendantes saillantes et dans la distribution de ces informations vers les centres cérébraux de contrôle cognitif descendant impliqués dans les processus de haut niveau. Le relai de l'information *bottom-up* se ferait

notamment par l'intégration des signaux viscéraux, lesquelles influenceraient la saillance subjective perçue (44, 173, 174). Ce réseau est bilatéral (174). De plus, plusieurs découvertes scientifiques s'accordent sur le rôle crucial que jouerait l'insula antérieure dorsale dans le 'switching' attentionnel entre deux larges réseaux neuronaux soit, d'une part le réseau du mode par défaut, impliquant le cortex préfrontal ventro-médian et le cortex cingulaire postérieur, avec pour fonction le traitement cognitif relié au soi et à la cognition sociale, et d'autre part, le réseau central exécutif régi par le cortex préfrontal dorso-latéral et le cortex pariétal postérieur, recruté lors de tâches orientées vers un but (173, 175).

2.4.4 Études en neuroimagerie

A l'aide de tâches attentionnelles de type *oddball*, des travaux en neuroimagerie ont mis en lumière une activation de l'insula suivant la présentation de stimuli intrinsèquement saillants et pertinents aux buts, corroborant son rôle dans le réseau de saillance (8, 46, 53, 82, 176-181). Hahn et ses collaborateurs (182) ont, quant à eux, nuancé ces affirmations en suggérant qu'elle serait impliquée dans la détection de stimuli saillants peu prédictibles. Par ailleurs, dû à ses communications réciproques avec le cortex frontal inférieur et le cortex cingulaire antérieur, plusieurs études s'accordent sur des implications de l'insula dans le traitement attentionnel plus élaborées qui s'étendraient à la mise à jour continue en mémoire de travail des informations saillantes internes et externes (183), à la détection des incongruences et des erreurs (184) et au processus d'inhibition lié aux interférences pour limiter les réponses inappropriées (183, 185-188). Toutefois, très peu d'évidence clinique appuie la présence de difficultés attentionnelles suivant des chirurgies d'épilepsie ou tumorale insulaire (189).

2.4.5 Synthèse III

L'ensemble de ces observations en neuroimagerie est compatible avec la position cruciale de l'insula dans le réseau de saillance. Toutefois, le rôle précis de chaque portion insulaire dans la dynamique spatio-temporelle du traitement de l'information saillante demeure inconnu, en raison notamment de la faible résolution temporelle des techniques en neuroimagerie. Bien que la combinaison des résultats en stimulation corticale et en neuroimagerie laisse supposer un traitement automatique des informations sensorielles opéré par la portion postérieure et un traitement volontaire pour l'information pertinente par la portion antérieure, cette assertion reste actuellement purement hypothétique. De plus, l'implication de l'insula dans l'orientation attentionnelle et dans le processus d'inhibition n'est suggérée qu'à travers son activation au sein de réseaux neuronaux incluant notamment le cortex cingulaire antérieur, rendant ainsi difficile à délimiter sa contribution individuelle, d'autant que très peu de résultats cliniques appuient ces données empiriques.

3. Épilepsie insulaire

3.1 Définition, rappel historique et sémiologie

L'épilepsie est une condition chronique caractérisée par des crises récidivantes et spontanées qui se manifestent par des décharges neuronales hyper-synchrones excessives et anormales, interrompant ainsi le fonctionnement normal du cerveau (190). Différentes causes étiologiques sont attribuées à l'épilepsie incluant les lésions acquises (accident vasculaire cérébrale, infection, hypoxie-ischémie périnatale et traumatisme crânien), les tumeurs cérébrales, les mutations génétiques, les malformations du développement cortical, les malformations vasculaires et les maladies neurodégénératives (191). Dépendamment de la localisation du foyer épileptogène, de l'intensité et de la propagation des crises, du contrôle des crises et de la durée de l'épilepsie, des conséquences néfastes pour l'individu peuvent se répercuter sur le fonctionnement cognitif et psychologique, ainsi que sur le statut socio-économique (190, 192).

Le concept d'épilepsie insulaire, introduit à partir du milieu du 20^{e} siècle, soulevait l'hypothèse que l'insula pouvait être générateur de crises, que les manifestations de crises insulaires pouvaient mimer celles des crises temporales et que la résection de l'insula était peut-être nécessaire pour le traitement de l'épilepsie de certains patients. Ce concept était notamment appuyé par la présence d'activités épileptiformes enregistrées dans le cortex insulaire par électrocorticographie pendant des chirurgies d'épilepsie du lobe temporal, ainsi que par la réplication de symptômes exprimés durant les crises d'épilepsie au moyen de stimulations électriques directes (78, 193, 194). Grâce à des données cumulatives au cours des 20 dernières années, il est maintenant clair que l'insula est en mesure de générer des crises et que le fait de ne pas les reconnaître est une source d'échec de chirurgie de l'épilepsie. La sémiologie initialement associée aux crises insulaires consistait à une

constriction laryngée, la paresthésie intra et péri-orale, des manifestations viscérales (incluant nausée et vomissement), des dysarthries langagières et des hallucinations auditives avec ou sans altération de l'état de conscience. Il est toutefois désormais bien établi que les manifestations cliniques des crises insulaires sont plus diverses incluant notamment des auras somatosensitifs, psychiques (anxiété, peur, gêne), olfacto-gustatifs, auditifs et vestibulaires pouvant évoluer vers des crises non-motrices ou hypermotrices. Cette variété de manifestations a fait dire à certains que l'insula était un grand imitateur, pouvant générer des symptômes mimant les épilepsies temporale, pariétale et frontale (56, 57, 79, 195-197).

3.2 Investigations cliniques

Une résection chirurgicale du foyer épileptogène peut être préconisée pour certaines épilepsies focales pharmaco-résistantes, en particulier si le foyer est opérable et que la chirurgie mènerait à une potentielle guérison complète ou à une réduction importante du nombre de crises (198). Le succès de la chirurgie est conditionnel à l'identification précise de la zone épileptogène (57, 196). L'identification de la zone épileptogène se fait dans une première étape par l'analyse de la sémiologie des crises et de tests non-invasifs tels l'imagerie par résonance magnétique (à la recherche d'une lésion épileptogène), l'EEG de surface (pour analyser la topographie des décharges épileptiformes), la magnétoencéphalographie (pour identifier les sources des changements magnétiques associées aux pointes épileptiformes), la tomographie par émission de positrons (pour identifier une zone hypométabolique anormale) ou la tomographie par émission monophotonique ictale (pour visualiser les zones d'hyperperfusion cérébrales au moment des crises). Cependant, il peut arriver que la localisation du foyer épileptogène avec les méthodes non-invasives conventionnelles se solde en échec, notamment dans le cas d'épilepsies insulaires (56, 196). D'ailleurs, certains échecs de chirurgies d'épilepsies présumées temporale, frontale et pariétale sont attribuées à une mauvaise

identification du foyer épileptogène, en réalité d'origine insulaire (199). Ainsi, le recours à une investigation en EEG intracrânienne (iEEG) est souvent préconisé dans les cas où l'insula est suspectée d'être le foyer à l'origine des crises. L'iEEG est une mesure électrophysiologique invasive qui nécessite le placement de plaques sous-durales positionnées en surface de l'insula et/ou d'électrodes intracrâniennes en profondeur implantées à l'intérieur de l'insula, par stéréotaxie ou par craniotomie. Contrairement à l'EEG de surface, l'iEEG s'affranchit de la distorsion du signal électrique due à la résistance du crâne et permet ainsi un enregistrement direct de l'activité neuronale (c.-à-d. les potentiels de champs locaux), et donc des crises épileptiques. Contrairement à l'EEG de surface, les positions des électrodes sont choisies de manière spécifique et individualisées pour chaque patient (156, 200).

3.3 IEEG et insula

L'iEEG offre une résolution spatiale comparable à celle obtenue en IRMf pour la région échantillonnée, de même qu'une résolution temporelle équivalente à l'EEG de surface, ce qui en fait un outil très performant dans l'étude fondamentale de structures cérébrales ciblées (156, 200). Les études sur l'insula menées avec l'iEEG ont mis en lumière le rôle de cette structure dans le traitement de stimuli affectifs lors de la présentation de mots, d'images et d'expressions faciales à caractère émotionnel, en particulier lorsque ces derniers étaient liés à l'émotion du dégoût ou à connotation négative, reflété par une réponse de l'insula autour de 200-300 ms mesurée en potentiel évoqué (201-203). Une autre étude plus récente de Cristofori et de ses collaborateurs (204) a rapporté la présence d'activité oscillatoire en fréquence thêta dans l'insula antérieure durant l'expérience d'une condition d'exclusion sociale associée à un gain monétaire, traduisant la compensation d'un sentiment négatif par un signe de récompense secondaire opérée par l'insula. La présence de fréquence gamma dans l'insula en réponse à une stimulation thermo-nociceptive autour de 150-300 ms post-stimulus a

également été rapportée (205). Toutefois, bien que ces études en iEEG apportent une contribution non-négligeable quant à la compréhension du rôle de l'insula dans le traitement de l'information, la couverture insulaire reste dans la majorité des cas limitée, rendant ainsi difficile à exposer la dynamique spatio-temporelle du traitement de l'information au sein de l'insula.

4. Proposition de recherche

4.1 Position de la problématique

Les sections précédentes ont mis en lumière une convergence d'indices issus de la recherche en neuroimagerie, en EEG de surface, ainsi qu'en études de lésion concernant l'implication de l'insula dans les fonctions sensorielles, vestibulaires et somato-motrices, ainsi que dans le traitement des informations émotionnelles et dans les fonctions attentionnelles. Toutefois, les découvertes scientifiques actuelles ont rapporté des résultats distincts et parfois disparates quant à l'implication de l'insula dans ces processus. Son rôle spécifique demeure à ce jour imprécis, notamment en raison des limitations des méthodes d'investigation couramment utilisées qui ne permettent pas de rendre compte de la dynamique spatio-temporelle du traitement de l'information au sein de l'insula, ainsi que la rareté des dommages circonscrits à l'insula. La contribution exclusive de chacune des portions insulaires au traitement attentionnel *bottom-up* et *top-down* n'a pour l'heure actuelle jamais été investiguée au moyen d'un enregistrement en temps réel et à sa source. Or, l'étude de l'insula au moyen d'électrodes directement implantées dans le cadre d'une évaluation pré-chirurgicale pour une épilepsie réfractaire permettrait de s'affranchir des limitations des méthodes traditionnelles. Par ailleurs, la résection insulaire partielle ou complète de l'insula chez les patients atteints d'épilepsie est de plus en plus préconisée depuis l'avènement des techniques de microchirurgie, d'autant qu'une amélioration considérable du contrôle des crises y est rattachée (57, 206, 207). Cependant, les séquelles neuropsychologiques résultant d'une insulectomie demeurent encore floues et très peu investiguées, notamment dans le traitement sensoriel et affectivo-attentionnel. L'étude de ces séquelles pourrait, d'autre part, contribuer à l'avancement des connaissances du rôle de l'insula dans le traitement de l'information.

4.2 Objectifs et hypothèses

L'objectif principal de cette thèse est de préciser la nature de la contribution de l'insula au traitement de l'information sensorielle, saillante, attentionnelle et émotionnelle à l'aide de mesures neurophysiologiques menées en iEEG auprès de patients dont des électrodes ont été implantées, notamment dans l'insula, pour l'investigation du foyer épileptogène en vue d'une chirurgie d'épilepsie, ainsi qu'au moyen d'évaluations cliniques auprès de patients ayant subi une insulectomie pour le contrôle de crises épileptiques pharmaco-résistantes.

Le premier objectif vise à documenter la contribution de chacune des portions insulaires au traitement attentionnel envers des informations visuelles et auditives. Les hypothèses de recherche sont: 1) *L'insula antérieure* répondrait à un stade tardif du traitement attentionnel, lors de la détection d'informations pertinentes auditives et visuelles, reflétant ainsi un traitement attentionnel volontaire de type *top-down*; 2) *L'insula postérieure* interviendrait à un stade précoce du traitement attentionnel, lors de la présentation d'informations saillantes auditives, pertinentes ou non à la tâche, traduisant alors un traitement attentionnel automatique de type *bottom-up*. Afin d'explorer ces conjectures, les réponses de l'insula lors de la présentation de stimuli pertinents, saillants et familiers, en modalité visuelle et auditive, sont enregistrées au moyen de l'iEEG auprès de 8 patients avec des électrodes implantées notamment dans l'insula dans le cadre d'une évaluation pré-chirurgicale pour une épilepsie pharmaco-résistante. Les données sont analysées en potentiel évoqué et en temps-fréquence.

Article 1: Citherlet, D., Boucher, O., Tremblay, J., Robert, M., Gallagher, A., Bouthillier, A., Lepore, F., & Nguyen, D. K. (2019). **Role of the insula in top–down processing: an intracranial EEG study using a visual oddball detection paradigm.** Brain Structure and Function, 224(6), 2045-2059.

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Article 2: Citherlet, D., Boucher, O., Tremblay, J., Robert, M., Gallagher, A., Bouthillier, A., Lepore, F., & Nguyen, D. K. (2020). **Spatiotemporal dynamics of auditory information processing in the insular cortex: an intracranial EEG study using an oddball paradigm.** Brain Structure and Function, 225(5), 1537-1559.

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Le second objectif vise à mieux comprendre les conséquences neuropsychologiques d'une insulectomie sur le traitement sensoriel et affectivo-attentionnel. Les hypothèses de recherche sont: 1) *Une résection insulaire* entraînerait des *difficultés dans le traitement multisensoriel* reflétées par des perturbations sensorielles dans le seuil de sensibilité et d'enregistrement, dans l'évitement des sensations, ainsi que dans la recherche sensorielle; 2) *Une résection insulaire* entraînerait des *difficultés attentionnelles* spécifiques aux informations affectives. La première étude est menée sur 17 participants ayant subi une résection partielle ou radicale de l'insula pour une épilepsie réfractaire. Le traitement sensoriel est évalué à l'aide du questionnaire du profil sensoriel de Dunn (AASP) (208). La seconde étude est conduite avec 16 patients ayant également subi une chirurgie d'épilepsie insulaire. Le traitement attentionnel et les capacités d'inhibition pour l'information affective sont évalués au moyen d'une tâche Dot-Probe révisée, ainsi qu'avec une version « émotionnelle » du test de Stroop. Pour les deux études, les réponses et les performances sont comparées à un groupe de lésion-contrôle constitué de sujets ayant subi une lobectomie temporale pour le contrôle des crises épileptiques, ainsi qu'à un groupe de sujets sains.

Article 3: Citherlet, D., Boucher, O., Hébert-Seropian, B., Roy-Côté, F., Gravel, V., Bouthillier, A., & Nguyen, D. K. (2020). **Sensory profile alterations in patients with insular epilepsy surgery: Preliminary findings.** Epilepsy & Behavior, 111, 107499.

Article publié : https://doi.org/10.1016/j.yebeh.2020.107499

Article 4 : Citherlet, D., Boucher, O., Gravel, V., Roy-Côté, F., Bouthillier, A., & Nguyen, D. K. (2020). **The effects of insular and mesiotemporal lesions on affective information processing: Preliminary evidence from patients with epilepsy surgery.** Epilepsy & Behavior, 111, 107264.

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CHAPITRE II : ÉTUDES EN EEG INTRACRÂNIEN

ARTICLE I

ROLE OF THE INSULA IN TOP-DOWN PROCESSING: AN INTRACRANIAL EEG STUDY USING A VISUAL ODDBALL DETECTION PARADIGM.

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Abstract

Functional neuroimaging studies suggest that the insular cortex – and more especially the anterior insula (aI) – is involved in attentional processes and plays a crucial role in the "salience network". However, its specific role in attentional processing remains unclear, which is partly attributable to the low temporal resolution of non-invasive neuroimaging techniques. This study aims to examine the spatio-temporal dynamics of visual target processing using intracranial EEG recorded directly from the insula. Eight epileptic patients (4 women, age 18 – 44 years) completed a three-stimulus visual oddball task during the extraoperative invasive intracranial EEG (iEEG) monitoring of their drug-resistant seizures. Depth electrodes were implanted in ten insular lobes (5 left, 5 right) and provided a total of 59 recording contacts in the insula. Event-related potentials (ERPs) and high-gamma-band responses (GBRs) were processed offline. Permutation analyses were performed to compare ERP signals across conditions during the P300 (225 – 400) interval, and modulations of GBRs (70-150 Hz) were computed for separate 100 ms time windows (from 0 to 1,000 ms poststimulus) and compared across conditions using non-parametric Wilcoxon test. Target stimuli were associated with a P300 (250 – 338 ms) component for 39 % of contacts implanted in the aI, most probably reflecting voluntary attentional processing. Amplitude was significantly greater for target than for standard stimuli for all of these contacts, and was greater than for novel stimuli for 72 %. In the posterior insula (pI), 16 % of contacts showed preferential responses to target stimulus in the P300 interval. Increased GBRs in response to targets were observed in 53 % of aI contacts (from ≈ 200-300 ms), and in 43 % of pI contacts (from ≈ 400-500 ms). This study is the first to characterize the spatiotemporal dynamics of visual target processing in the insula using iEEG. Results suggest that visual targets elicit a P300 in the aI which corresponds in latency to the P3b component, suggesting that this region is involved in top-

down processing of task-relevant information. GBRs to visual targets occur earlier in the aI than in the pI, further characterizing their respective roles in voluntary attentional processing.

Short running head: Visual P300 and high-gamma activity in the human insula

Keywords: Attention; Insula; Intracranial EEG; Orienting response; P300; High-gamma; Salience network; Target; Top-down; Visual oddball

Introduction

The insula (Island of Reil) is considered as the fifth lobe of the brain. This paralimbic structure is localized deep in the Sylvian fissure, enclosed by the frontal, parietal, and temporal opercula. It is divided into two portions by the central insular sulcus: the anterior insula (aI) and the posterior insula (pI). The aI is composed of three short gyri (anterior, middle, and posterior short gyri), and the pI is made of two long gyri (anterior and posterior long gyri) (Türe et al., 1999). The insula has been associated with a large variety of functions, including sensory (visceral, somatosensory, auditory, gustatory, and olfactory), affective (emotions, empathy), and cognitive (language, attention, decision-making) processing (Uddin et al., 2017). It has also been proposed to be involved in autonomic and vestibular functions (Mazzola et al., 2014; Oppenheimer et al., 1992) and might be crucial for interoception (Craig, 2003). However, its specific role(s) remain(s) enigmatic, which is partly attributable to its location which makes it difficult to access, and to the very rare prevalence of brain damage restricted to the insular cortex (Cereda et al., 2002).

Functional neuroimaging studies have revealed a functional differentiation within the insular lobe, with the aI being activated during cognitive and socio-emotional tasks, and the pI, by sensorimotor and chemosensory stimuli. More specifically, results from a meta-analysis of 1,768 neuroimaging studies suggest that the anterior-dorsal region of the insula is activated during tasks assessing attention and working memory (Kurth et al., 2010). Indeed, activation of the aI has been reported in response to multimodal target detection and during goal-directed tasks (Clark et al., 2000; Downar et al., 2000; Kiehl et al., 2001; Linden et al., 1999; Nelson et al., 2010; Stevens et al., 2000). It has been suggested that the insular cortex is involved, along with other brain areas (e.g., supramarginal gyrus, frontal operculum, superior parietal lobule and anterior cingulate cortex) in a "target detection network" which is used in the detection of visual target stimuli (Ardekani et al.,

2002; Clark et al., 2000). More recently, the aI, along with the dorsal anterior cingulate cortex and subcortical and limbic structures, has been put in the core of the "salience network", which enables the attentional focus on the most salient stimuli in the environment (Menon & Uddin, 2010; Uddin, 2015). Currently, it remains unclear whether the aI participates in the voluntary (top-down) or automatic (bottom-up) detection of salient information, or in both processes.

Electroencephalography (EEG) studies have showed that the automatic and the voluntary/controlled processes involved in change detection can be distinguished both temporally and spatially. On scalp EEG, detection of an attended and unpredictable target stimulus is associated with an event-related potential (ERP) component peaking around 300-400 ms poststimulus and maximal over the centro-parietal region. This positive-amplitude component, referred to as the P3b, reflects deliberate attentional processing for a relevant and expected stimulus. By contrast, novel task-irrelevant stimuli are associated with the P3a, which occurs 225-300 ms post-stimulus and maximal in the frontal region (Ardekani et al., 2002; Polich, 2007; Posner, 1980; Snyder & Hillyard, 1976; Squires et al., 1975). The P3b subcomponent occurs independently of the modality, and tends to occur later in response to visual compared to auditory targets (Snyder et al., 1980). Both the P3a and the P3b components can be elicited during an oddball detection paradigm. Several electrophysiological studies using electrical sources localization by low-resolution electromagnetic tomography (LORETA) have helped characterizing the scalp topography and cortical sources of the P300 subcomponents. According to these studies, generators of the P3b include the insula, the temporal-parietal junction, the superior temporal gyrus, the dorsolateral prefrontal cortex (Mulert et al., 2004), the temporo-occipital regions, and the limbic as well as the anterior cingulate region (Volpe et al., 2007), whereas the generators of P3a are localized in cingulate region, frontal and right parietal areas (Volpe et al., 2007). A few studies using invasive intracranial EEG (iEEG) recordings with epileptic

patients have showed P3a ERP responses to deviant stimuli located along the cingulate gyrus, the inferior frontal sulcus, the temporo-parietal cortex, the inferior temporal gyrus, and the posterior parahippocampus, and P3b ERP responses in the hippocampus, superior temporal sulcus, ventrolateral prefrontal cortex and intraparietal sulcus (Baudena et al., 1995; Halgren et al., 1995a, b; 1998). To our knowledge, no study has yet described P3a or P3b components in the insula, which may be attributed to rare and/or incomplete sampling of this region in these studies.

Beyond its higher localization value, one major advantage of intracranial over scalp EEG recording is the ability to measure signals in high frequencies (Parvizi & Kastner, 2018). Several studies have showed that high frequency (> 40Hz) iEEG activity allows the investigation of task-related neural processes with high anatomical, temporal and functional specificity (e.g., Lachaux et al., 2012). Increased activity in the high-gamma-frequency range (60-150 Hz) has been observed during functional activities in a variety of sensory and cognitive functions including sensorimotor, auditory, visual, attentional processing, memory, learning and language, in both sensory and non-sensory areas (Jensen et al., 2007; Lachaux et al., 2012; Ray et al., 2008; Ward, 2003). More specifically, gamma-frequency modulation has been proposed to serve as a mechanism for active maintenance of representations in working memory, underlying the neuronal substrate for directed attention (Jensen et al., 2007). A scalp-EEG study has showed that gamma-band frequency differed between target and non-target stimuli processing during an auditory oddball task. A late oscillatory activity peaking at 37 Hz around 360 ms was observed only after target stimuli, suggesting gamma-band frequency involvement in voluntary attentional function (Gurtubay et al., 2001). In a subdural electrocorticography study in humans, high-gamma modulation (80-150 Hz) was described from around 400 ms after stimulus onset in sensory and prefrontal cortices during a selective attentional task (Ray et al., 2008). More recently, intracranial electroencephalography recordings in epileptic

patients have showed a modulation of high-frequency activity (70-150 Hz) in response to affective information, linking high-gamma modulation to saliency information processing (Boucher et al., 2015). Currently, very few studies have reported a high-gamma modulation in the insular cortex linked to attentional processing (e.g., Müsch et al., 2014). To our knowledge, no study has yet evaluated the spatio-temporal dynamics of attentional processing in the high-gamma-frequency range within the insular cortex.

In recent years, the insula has been recognized as a possible seizure focus in a nonnegligible proportion of epileptic patients (Isnard et al., 2004; Nguyen et al., 2009; Obaid et al., 2017). Because of the widespread connections that the insula shares with other brain areas (Ghaziri et al., 2017), insular seizures are difficult to diagnose as they can mimic other more common types of epilepsies such as mesial temporal lobe epilepsy and frontal lobe epilepsy. Therefore, invasive iEEG recordings are often required in patients undergoing epilepsy surgery for whom an insular focus is suspected (Surbeck et al., 2011). Intracranial EEG offers a unique opportunity to study the role of the insula in information processing, by combining the excellent temporal resolution of EEG with a spatial resolution comparable to that of functional magnetic resonance imaging (fMRI) (Lachaux et al., 2003). In the present study, we use iEEG to examine the spatio-temporal dynamics of information processing in the insular cortex. More especially, this study aims to determine whether the insula is involved in the controlled/voluntary detection of task-relevant information (top-down processing), in the automatic detection of new information (bottom-up processing), or both, and whether this differs across insular subregions.

Experimental procedure

Participants

Eight epileptic patients (four female; mean age = 30.6, range = 18 – 44 years, all right-handed) with drug-resistant seizures, hospitalized for long-term extraoperative invasive iEEG monitoring to better delineate their epileptic focus, were recruited for the present study. Testing occurred at least three days after intracranial electrodes implantation. All patients gave their informed written consent to participate to the experiment. The study was approved by the CHUM ethics committee, and was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki. Table 1 summarizes characteristics of the study participants. A total of 59 electrode contacts were implanted in ten insulae (5 left, 5 right).

Oddball task

A three-stimulus visual oddball detection paradigm was employed to study attentional processing in the insula. Patients were tested in their hospital room and seated approximately 57 cm from the computer screen. Participants were instructed to keep their gaze on a cross localized at the center of the screen, and to press the space key on the keyboard as quickly as possible in response to the target stimulus (blue square, 8x8 cm, 15% probability), and not to press in response to the standard (red square, 8x8 cm, 70%) and novel (green square, 8x8 cm, 15%) stimuli. Each block contained 70 standard stimuli, 15 target stimuli, and 15 novel stimuli. The total task includes six blocks of 100 stimuli presented in a pseudorandomized order. Stimulus duration was 50 ms and was presented centrally on a black background. Inter-stimuli interval was fixed at 2,000 ms. Participants

Tableau 1. – Descriptive characteristics of the study participants

Pt. #	Gender	Age (yrs)	Age at 1st seizure (yrs)	Implanted regions	Total no. of recording contacts	No. of contacts for analysis	No. of contacts in the insula	Seizure focus
1	F	18	10	L (F, P, T, I)	116	113	6	L Anterior insula
2	M	22	10	L (P, T, I)	110	110	3	Not determined
3	M	23	11	L (F, T, I) and R (F, T, I)	113	101	11	Bitemporal (Hippocampus)
4	M	34	20	R (F, P, T, I)	116	110	4	R Frontal
5	F	32	30	L (F, T, P, I, O)	116	111	11	L temporo-insular
6	F	37	23	L (C, F, P, I) and R (C, F, P, I)	101	95	19	R Cingular cortex
7	F	35	21	R (F, I, T)	84	82	2	R Operculo-orbito-insular
8	M	44	12	R (F, I, T)	94	92	3	R Middle and inferior frontal gyri junction

Abbreviations. R, right; L, left; F, frontal; I, insula; P, parietal, O, occipital; T, temporal; C, cingulate

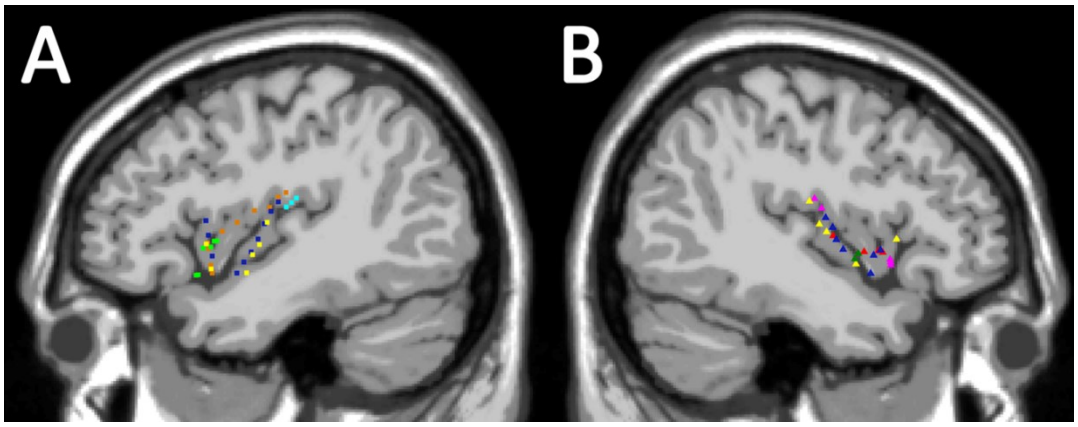
were offered a short pause between each block. Visual stimuli were presented on a 17 in. display monitor using Presentation software v. 14.5 (neurobehavioral systems: http://www.neurobs.com).

IEEG recording and analyses

Intracranial EEG acquisition was performed at 2 kHz using a Stellate Harmonie audio-video-EEG monitoring system (Natus Medical, San Carlos, CA), by means of depth electrodes, subdural strips and grid electrodes (Ad-tech medical instruments, Racine, WI), with one mastoid used as reference and the other used as ground.

A 3D reconstruction with Stellate Gridview software was performed on postimplantation MRIs for localization of electrode contacts. Stellate Gridview coordinates were transformed to Talairach coordinates to allow an automatic localization of contacts according to the Talairach Daemon atlas (Lancaster et al., 2000), for visualization purposes. The distribution of the insular electrode contacts from the eight patients is illustrated in Figure 1. A total of 59 contacts in the insula were analyzed in the present study.

Figure 1. – Distribution of insular electrode contacts in our study participants (N = 8) according to the estimated Talairach coordinates, for the left (A) and right (B) hemispheres. Different colors were used to represent each patient: Pt. 1: green; Pt. 2: cyan; Pt. 3: yellow; Pt. 4: red; Pt. 5: brown; Pt. 6: blue; Pt. 7: dark green; Pt. 8: magenta.



EEG data were analyzed offline using Brain Vision Analyzer 2.0.1 software (Brain Products, Munich, Germany). All signals were down-sampled offline to 500 Hz. A visual inspection of raw data was applied. Channels with artefacts due to noise and epileptic activity on the whole signal were removed from further analyses (36/850, 4.2 %, see Table 1). Automatic artefact rejection (± 300 µV), maximal allowed voltage step (30 to 60 µV/ms), and manual inspection of the data were performed to remove epochs containing noise and epileptic activity. We excluded on average 9.63 % (between 3.39 % and 18.86 %) of data for each subject. Trials with errors and with responses occurring before 200 or after 2.000 ms following target-stimulus presentation were excluded.

ERP analysis

Data were segmented (-200 to 1,000 ms post-stimulus onset) separately for target, standard, and novel stimuli, and a baseline correction was applied (-200 ms). We used high and low pass filters at 0.1 and 30 Hz as usually applied for studying the P300 components (e.g., Demiralp et al., 2001; Guger et al., 2011; Lindin et al., 2004), with a 60 Hz notch filter to limit the influence of power-line noise present in North America. Automatic peak detection was used to measure P300 amplitude (most positive point between 225-400 ms poststimulus-interval) and P300 latency (relative to stimulus onset). Only the components in the P300 latency range (i.e., 225-400 ms) were considered for future analysis. Visual inspection of the averaged ERP data did not reveal any other obvious amplitude difference in the 0-1000 ms post-stimulus interval. More than 75 % of trials per condition were kept for analyses on average. However, only 21% of novel, 68% of standard and 54% of target trials were conserved for one patient (Pt. #6). To this fact, results for this participant have had to be interpreted with this limitation. This procedure was performed using Brain Vision Analyzer 2.0.1 software.

GBR analysis

Data were segmented (-500 to 1,500 ms post-stimulus onset) separately for target, standard, and novel stimuli. Continuous time-frequency analysis over each trial was performed using complex Gaussian Morlet's wavelet in the frequency range of 70-150 Hz, in eight separate 10 Hz linear steps. The Morlet parameter was set at seven. A baseline correction (-200 to -50) was applied. We decided to select this frequency band based on previous works that used 70-150 Hz band-frequency to study intracranial gamma-band responses (Boucher et al., 2015; Vidal et al., 2010). This procedure was performed using Brain Vision Analyzer 2.0.1 software.

Due to epileptic focus in the insula and several seizures during the testing, we excluded one subject (Pt. # 5) from GBR analysis to avoid skewing our results with high-gamma activity originating from epileptic discharges. We kept on average 72% of trials for each subject, except for one (Pt. # 6) for whom only 18% of novel, 26% of target and 59% of standard trials were conserved. At this step, we decided to exclude these two subjects for GBR analyses.

A broadband 70-150 Hz gamma-band power was computed, using a normalization method described earlier (Boucher et al., 2015) allowing for correction of the power decrease of the signal with increasing frequency due to the fact that event-related GBRs are broadband (Lachaux et al., 2012). For the eight separate frequency bands (10 Hz each one, from 70-80 Hz to 140-150 Hz), power value for a given time interval were divided by the median value, on the same frequency band, from all the prestimulus baseline epochs. Broadband activity was computed by calculating the average of those eight normalized frequency layers. Epochs with outliers value (>3.29 SD from the mean) were excluded. This procedure was repeated for each time interval, including the baseline (-200 to -50 ms) and for every 100 ms intervals (from 0 to 1,000 ms poststimulus). These values obtained represent the mean broadband gamma power over a time interval of 100 ms duration, expressed as the

percentage of power change relative to baseline level for each insular contact. This procedure was performed using MatLab software (R2015a).

Statistical analysis

ERPs

Nonparametric permutation tests (Galán et al., 1997) were performed (1,000 permutations) using MatLab software (R2015a). Electrode contacts showing a significant ($p < 0.001$) amplitude difference between the 225-400 ms interval at the baseline following target and/or novel stimuli were first identified. Then, for each of these contacts, permutation tests were performed to test for amplitude difference in the 225-400 ms interval between each pair of condition (i.e., target vs. standard; novel vs. standard; target vs. novel). At this step, a $p < 0.05$ criterion was used. Bonferroni correction was applied in order to avoid spurious positive results due to number of comparisons being performed for each electrode. We divided the alpha value criterion by the number of comparisons (i.e., target vs. standard; novel vs. standard; target vs. novel). Thus, a $p < 0.017$ criterion was used for each contact.

GBRs

Electrode contacts showing a significant response ($p < 0.001$) in the high gamma band associated with presentation of target and/or novel stimuli were identified using Wilcoxon signed-rank tests comparing gamma-band power during each poststimulus time interval to that of the prestimulus baseline epoch (-200 to -50 ms) on the same trial. Then, for each significant GBR identified for target and/or novel condition (i.e., each poststimulus 100 ms time interval different from its baseline at the same contact), Mann-Whitney nonparametric tests were conducted to compare this GBR with each pair of condition (i.e., target vs. standard; novel vs. standard; target vs. novel). At this

step, a $p < 0.05$ criterion was used. As previously, Bonferroni correction was applied for each contact ($p < 0.017$). All analyses were conducted in Matlab software (R2015a).

Results

Behavioral results

Performance on the visual oddball task is summarized in Table 2. The task was well executed by all patients, as all of them responded to more than 75% of targets and to ≤ 1 % of non-targets. Mean reaction time differed strongly across participants. Patients who had slower hit reaction times (i.e., Pts. # 6 and 7) were also those with the lower hit detection rates.

Tableau 2. – Behavioral results on the visual oddball task

Pt. #	No. blocks completed (/6)	% hits	% false alarms	Mean ± SD hit RT (ms)
1	5	100.0	0.0 %	448 ± 66
2	6	98.9	0.0 %	412 ± 57
3	6	98.9	1.1 %	444 ± 78
4	6	100.0	0.0 %	395 ± 40
5	6	100.0	0.0 %	297 ± 34
6	4	76.7	0.0 %	537 ± 128
7	4	83.3	0.0 %	553 ± 141
8	6	95.6	0.0 %	434 ± 67

IEEG results

ERPs

Target stimuli elicited a P300 response for 11/28 of aI contacts (39 %) (i.e., 4/6 patients with aI contacts) (Pt. # 1, 3 contacts; Pt. # 3, 3 contacts; Pt. # 4, 3 contacts and Pt. # 6, 2 contacts, see Table 3). Amplitude was significantly greater for targets than for standard stimuli for all of these contacts

(100 %), and was significantly greater than for novel stimuli for 8/11 contacts (72 %) (Pt. # 1, 3 contacts; Pt. # 3, 2 contacts and Pt. # 4, 3 contacts). Significant responses to target stimuli were observed at left (6/18, 33 %) and at right (5/10, 50 %) anterior insular electrode contacts. In patients with bilateral insular coverage, P300 latency was comparable for left and right aI contacts.

By contrast to aI responses, target stimuli elicited significant P300 responses in only 5/31 of pI contacts (16%) (Pt. # 2, 3 contacts; Pt. # 4, 1 contact; Pt. # 6, 1 contact). Amplitude was significantly greater for targets than for standard stimuli for 3/5 contacts (60 %) (Pt. # 2, 2 contacts and Pt. # 6, 1 contact), and was significantly greater than for novel stimuli for 3/5 contacts (60 %). (Pt. # 2, 3 contacts). All of these contacts were localized in the left hemisphere. The distribution of significant insular electrode contacts from the eight patients is illustrated in Figure 2 and examples of P300 component recorded in the aI, and the grand average ERP for all aI contacts showing a significant P300 effect in response to target stimuli in the aI, are illustrated in Figure 3. Unlike target stimuli, novel (non-deviant target) stimuli did not elicit a significant P300 response in the insular cortex (Table 4).

Figure 2. – Distribution of the insular electrode contacts showing a significant increase in P300 amplitude in response to target vs. standard and/or novel stimuli (both hemispheres combined). Different colors were used to represent each patient: Pt. 1: green; Pt. 2: cyan; Pt. 3: yellow; Pt. 4: red; Pt. 6: blue. White color: non significant insular electrode contacts.

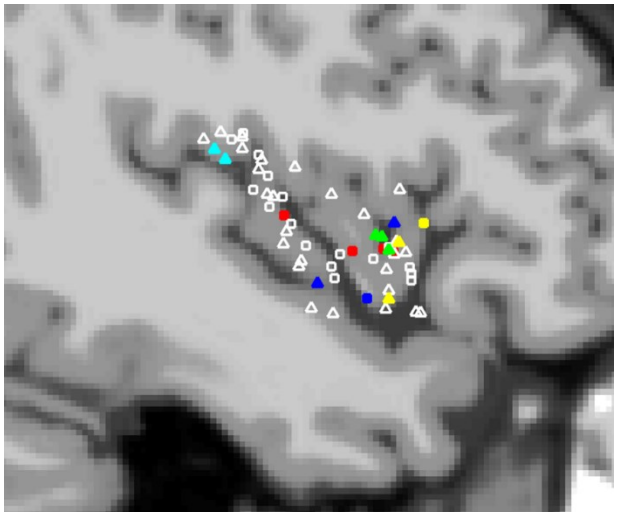


Figure 3. – Examples of P300 component recorded in the aI. A = Pt. 1, B = Pt. 3, C = Pt. 4, D = Pt.6, E = Grand average ERP for all aI contacts showing a significant P300 effect for target vs. standard stimuli. All significant contacts for a given participant were averaged prior to perform the grand average analysis, so that each participant has the same weight in the resulting ERP (blue: target, red: novel and dark: standard).

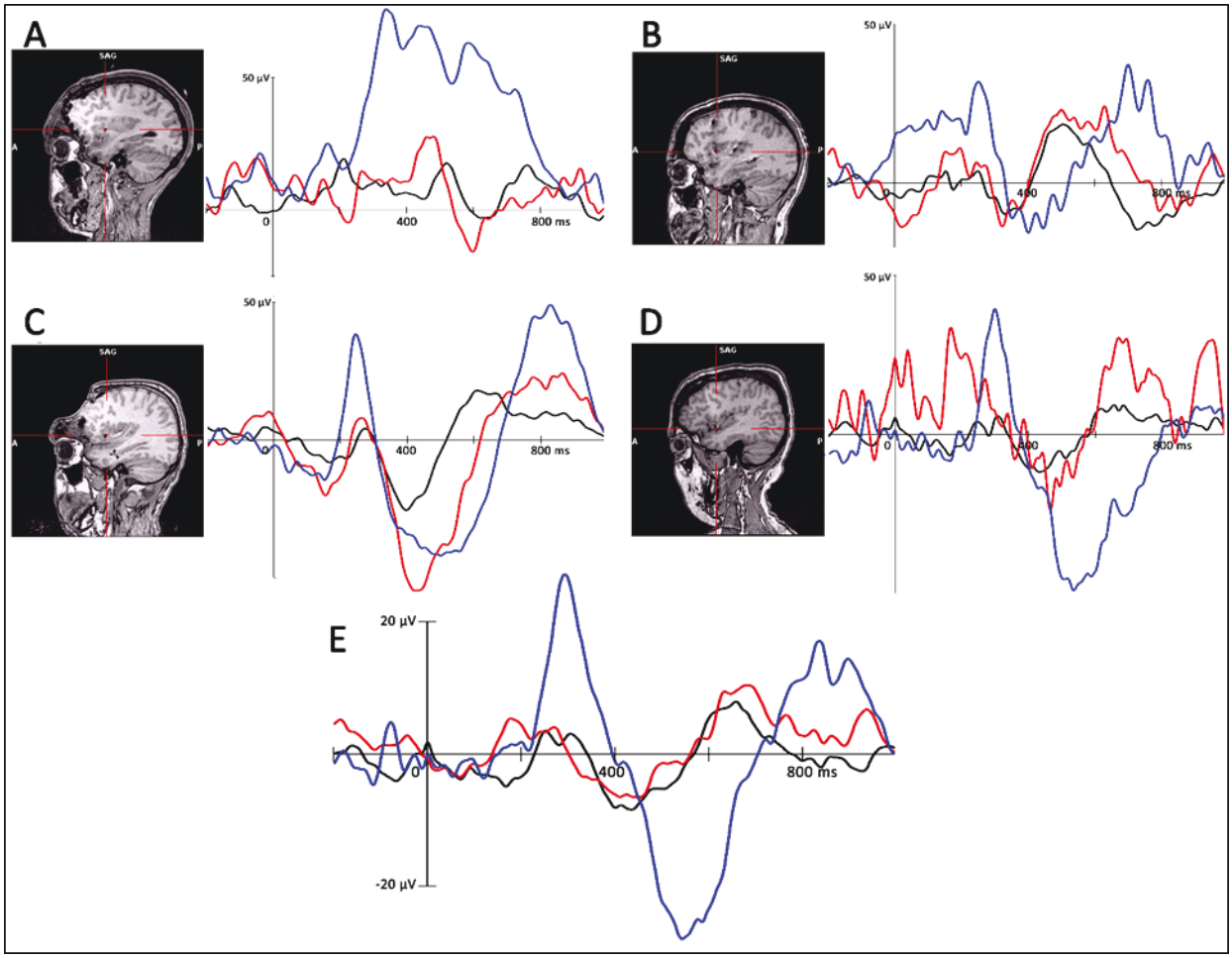


Tableau 3. – P300 (225-400 ms) responses to visual target recorded in the insula

Pt. #	Anterior insula						Posterior insula					
	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison
1	u11	Left	as-aps	338 ms	60 µV	T>S*; T>N*						
	u12	Left	as	-	-	-						
	u13	Left	as	-	-	-						
	u31	Left	as	330 ms	47.54 µV	T>S*; T>N*						
	u32	Left	as	332 ms	52.36 µV	T>S*; T>N**						
	u52	Left	as	-	-	-						
2							u32	Left	al	326 ms	19.17 µV	T>N**
							u33	Left	al	326 ms	29.51 µV	T > S*; T>N*
							u34	Left	al	326 ms	23.33 µV	T > S*; T>N*
3	u11	Left	as-ia	284 ms	20.94 µV	T>S*; T>N**	u31	Left	pcs	-	-	-
	u12	Left	as	252 ms	31.55 µV	T>S*	u32	Left	pcs	-	-	-
	u21	Right	as-ms	270 ms	16.35 µV	T>S**; T>N**	u33	Left	al	-	-	-
							u34	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
4	u22	Right	as	260 ms	23.71 µV	T>S*; T>N*	u42	Right	pl	276 ms	14.50 µV	n.s
	u23	Right	as	252 ms	22.41 µV	T>S*; T>N**						
	u24	Right	as	250 ms	39.77 µV	T>S*; T>N**						
5	u13	Left	as	-	-	-	u31	Left	al	-	-	-
	u14	Left	as	-	-	-	u32	Left	al	-	-	-
	u15	Left	as	-	-	-	u33	Left	al	-	-	-
	u16	Left	as	-	-	-	u34	Left	pl	-	-	-
	u17	Left	as	-	-	-						
	u35	Left	ms	-	-	-						
	u36	Left	as	-	-	-						
6	u11	Left	sis	-	-	-	u31	Left	cs	-	-	-
	u12	Left	ms-sis	298 ms	36.89 µV	T>S*	u32	Left	cs-li	304 ms	28.30 µV	T>S**
	u13	Left	ms-sis	-	-	-	u33	Left	al	-	-	-
	u21	Right	as-ia	298 ms	39.41 µV	T>S**	u34	Left	al	-	-	-
	u22	Right	ms-sis	-	-	-	u35	Left	al	-	-	-

	u23	Right	ms-sis	-	-	-	u36	Left	al	-	-	-
							u37	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
							u45	Right	al	-	-	-
							u46	Right	al	-	-	-
7							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
8	u22	Right	as	-	-	-						
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						

Abbreviations. T = Target; S = Standard; N = Novel; n.s = non significant; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the P300 interval in comparison to baseline are identified with a '-'sign.

*p-value < 0.001

**p-value < 0.01

Tableau 4. – P300 (225-400 ms) responses to novel stimuli in the insular cortex

Pt. #	Anterior insula						Posterior insula					
	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison
1	u11	Left	as-aps	-	-	-						
	u12	Left	as	-	-	-						
	u13	Left	as	-	-	-						
	u31	Left	as	-	-	-						
	u32	Left	as	-	-	-						
	u52	Left	as	-	-	-						
2							u32	Left	al	-	-	-
							u33	Left	al	-	-	-
							u34	Left	al	-	-	-
3	u11	Left	as-ia	-	-	-	u31	Left	pcs	-	-	-
	u12	Left	as	-	-	-	u32	Left	pcs	-	-	-
	u21	Right	as-ms	-	-	-	u33	Left	al	-	-	-
							u34	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
4	u22	Right	as	-	-	-	u42	Right	pl	-	-	-
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						
5	u13	Left	as	-	-	-	u31	Left	al	-	-	-
	u14	Left	as	-	-	-	u32	Left	al	-	-	-
	u15	Left	as	-	-	-	u33	Left	al	-	-	-
	u16	Left	as	-	-	-	u34	Left	pl	-	-	-
	u17	Left	as	-	-	-						
	u35	Left	ms	-	-	-						
	u36	Left	as	-	-	-						
6	u11	Left	sis	-	-	-	u31	Left	cs	-	-	-
	u12	Left	ms-sis	-	-	-	u32	Left	cs-li	-	-	-
	u13	Left	ms-sis	-	-	-	u33	Left	al	-	-	-
	u21	Right	as-ia	-	-	-	u34	Left	al	-	-	-

	u22	Right	ms-sis	-	-	-	u35	Left	al	-	-	-
	u23	Right	ms-sis	-	-	-	u36	Left	al	-	-	-
							u37	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
							u45	Right	al	-	-	-
							u46	Right	al	-	-	-
7							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
8	u22	Right	as	-	-	-						
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						

Abbreviations. T = Target; S = Standard; N = Novel; n.s = non significant; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the P300 interval in comparison to baseline are identified with a '-'sign.

GBRs

In total, 8/15 aI contacts (53 %) showed GBRs to target stimulus (Table 5). An early- and long-lasting (≈ 200-300 ms to 700 ms) target-dependent modulation of GBR was first observed for 7/15 of aI contacts (47 %) (i.e., 4/4 patients with aI contacts) (Pt. # 1, 1 contact; Pt. # 3, 1 contact; Pt. # 4, 3 contacts and Pt. # 8, 2 contacts). More specifically, target-stimulus presentation was associated with increased GBRs in comparison to both standard and novel stimuli for all of these contacts (100 %). A late- and short-lasting (from 600 ms to 700 ms) target-dependent modulation of GBRs was also recorded in one aI contact (1/15, Pt. # 8). Significant responses to target stimuli were observed at left (2/8, 25 %) and at right (6/7, 86 %) anterior insular contacts.

A later (≈ 400-500) modulation of gamma-band activity was observed in the pI in response to target stimulus for 5/14 contacts (36 %) (i.e., 2/4 patients with pI contacts) (Pt. # 2, 3 contacts and Pt. # 3, 2 contacts). Target stimulus was associated with increased high-gamma activity in comparison to both standard and novel stimuli for all of these contacts (100 %) exclusively located in the left hemisphere. An early- and long-lasting (from 200 ms to 900 ms) target-dependent modulation of GBRs was recorded in one pI contact (1/14, Pt. # 4). In total, 6/14 pI contacts (43 %) showed GBRs to target stimulus (Table 5).

Three aI contacts out of fifteen (20 %) showed a novel-dependent modulation of GBRs (i.e., 2/4 patients with aI contacts) (Pt. # 4, 2 contacts and Pt. # 8, 1 contact). For each of these contacts, high-gamma power was stronger for novel than standard stimuli (see Table 6). Significant responses to novel stimuli were exclusively located in the right hemisphere.

Figure 4 depicts the distribution of insular contacts showing significant stimulus-dependent gamma-band modulations (A), along with examples of GBRs recorded in the aI (B) and pI (C).

Figure 4. – Distribution of insular contacts showing significant high-gamma modulation in response to target stimuli (both hemispheres combined; yellow: aI and blue: pI) (A) and the average of significant contacts showing high-gamma activity, relative to baseline, in the aI (B) and pI (C) , across conditions (blue: target, red: novel and dark: standard).

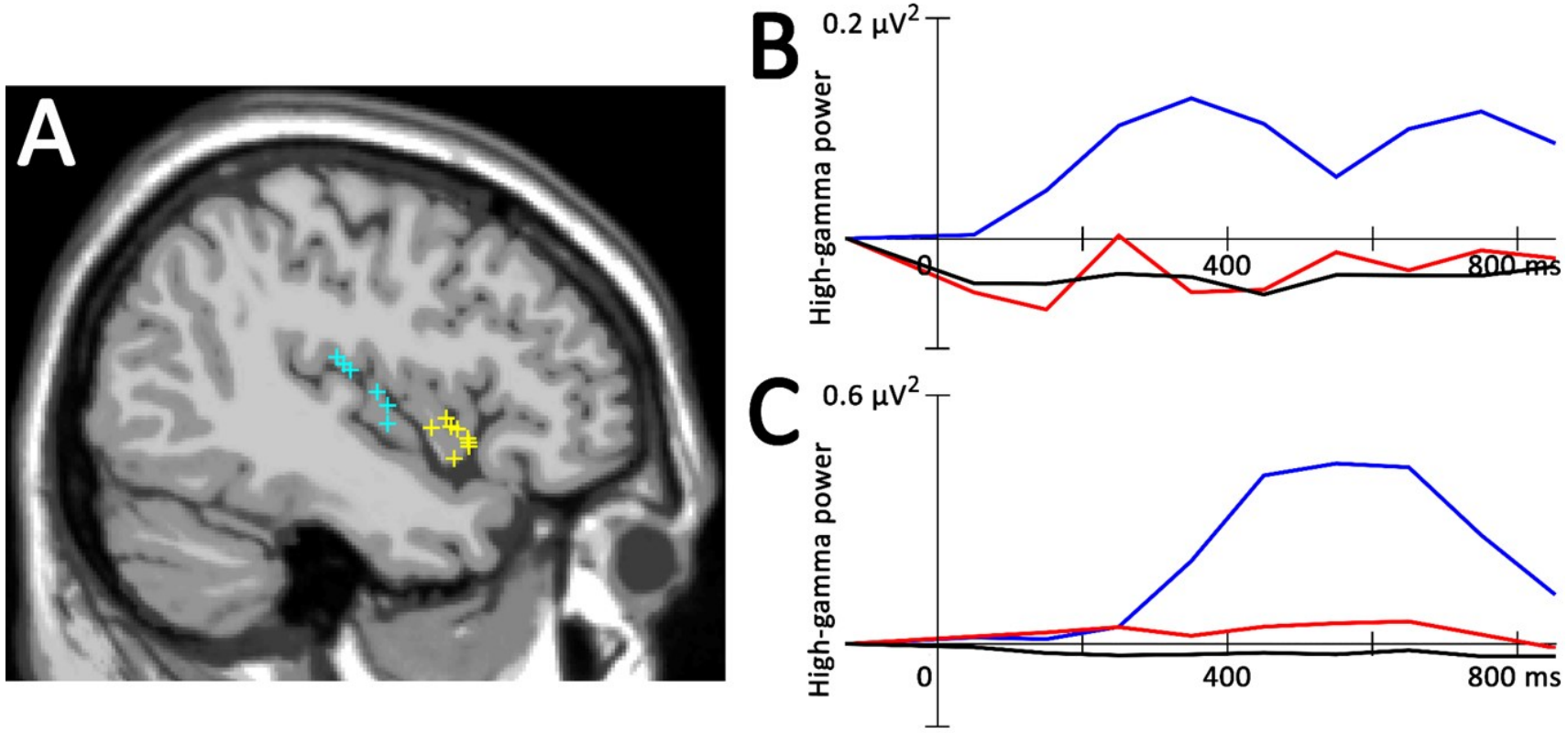


Tableau 5. – High-gamma modulations (70-150 Hz) in response to visual target recorded in the insula

Pt. #	Anterior insula					Posterior insula				
	Contact	Hemisphere	Gyrus	Comparison	Timing (ms)	Contact	Hemisphere	Gyrus	Comparison	Timing (ms)
1	u11	Left	as-aps	-	-					
	u12	Left	as	-	-					
	u13	Left	as	-	-					
	u31	Left	as	-	-					
	u32	Left	as	-	-					
	u52	Left	as	T>S; T>N	400-600 ms					
2						u32	Left	al	T>S; T>N	600-700 ms
						u33	Left	al	T>S; T>N	400-700 ms
						u34	Left	al	T>S; T>N	400-700 ms
3	u11	Left	as-ia	T>S; T>N	200-300 ms	u31	Left	pcs	-	-
	u12	Left	as	-	-	u32	Left	pcs	-	-
	u21	Right	as-ms	-	-	u33	Left	al	T>S; T>N	600-800 ms
						u34	Left	al	T>S; T>N	500-1,000 ms
						u41	Right	al	-	-
						u42	Right	al	-	-
						u43	Right	al	-	-
						u44	Right	al	-	-
4	u22	Right	as	T>S; T>N	200-800 ms	u42	Right	pl	T>S; T>N	200-900 ms
	u23	Right	as	T>S; T>N	200-500 ms					
	u24	Right	as	T>S; T>N	200-500 ms					
7						u41	Right	al	-	-
						u42	Right	al	-	-
8	u22	Right	as	T>S; T>N	400-800 ms					
	u23	Right	as	T>S; T>N	300-900 ms					
	u24	Right	as	T>S; T>N	600-700 ms					

Abbreviations. T = Target; S = Standard; N = Novel; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

All significant contacts showed a p-value < 0.01

Tableau 6. – High-gamma modulations (70-150 Hz) in response to novel stimuli in the insular cortex

Pt. #	Anterior insula					Posterior insula				
	Contact	Hemisphere	Gyrus	Comparison	Timing (ms)	Contact	Hemisphere	Gyrus	Comparison	Timing (ms)
1	u11	Left	as-aps	-	-					
	u12	Left	as	-	-					
	u13	Left	as	-	-					
	u31	Left	as	-	-					
	u32	Left	as	-	-					
	u52	Left	as	-	-					
2						u32	Left	al	-	-
						u33	Left	al	-	-
						u34	Left	al	-	-
3	u11	Left	as-ia	-	-	u31	Left	pcs	-	-
	u12	Left	as	-	-	u32	Left	pcs	-	-
	u21	Right	as-ms	-	-	u33	Left	al	-	-
						u34	Left	al	-	-
						u41	Right	al	-	-
						u42	Right	al	-	-
						u43	Right	al	-	-
						u44	Right	al	-	-
4	u22	Right	as	N>S	200-500 ms	u42	Right	pl	-	-
	u23	Right	as	N>S	300-500 ms					
	u24	Right	as	-	-					
7						u41	Right	al	-	-
						u42	Right	al	-	-
8	u22	Right	as	-	-					
	u23	Right	as	N>S	400-500 ms					
	u24	Right	as	-	-					

Abbreviations. T = Target; S = Standard; N = Novel; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

All significant contacts showed a p-value < 0.01

Discussion

This study examined the contribution of the human insula to visual target stimulus detection, using iEEG recordings in epileptic patients. A significant proportion (39 %) of aI contacts showed a significant ERP response following target stimuli occurring around 300 ms post-stimulus, most of which showed significantly greater response to targets than to both standard and novel stimuli, presumably reflecting a voluntary and controlled attention (i.e., top-down) effect. The results highlight the participation of the aI in the genesis of the P3b subcomponent, and also support an aI involvement in target detection as previously suggested by fMRI (Ardekani et al., 2002; Nelson et al., 2010) and scalp-EEG studies (Linden et al., 1999; Milner et al., 2014; Mulert et al., 2004). By contrast, a weak proportion (16 %) of pI contacts responded preferentially to visual target stimuli, a result which is congruent with the functional differentiation within the insula as revealed by previous studies (e.g., Kurth et al., 2010). A high proportion of aI contacts (53 %) also showed early modulations of high-frequency signal in response to target stimuli, which highlights a top-down processing as previously suggested by an iEEG study (Müsch et al., 2014). Contrarily to our expectations, a significant proportion (43 %) of pI contacts also showed GBRs to target stimulus starting around 400 ms. To our knowledge, our study is the first to characterize the P300 component and associated high-gamma modulations in the human insula using iEEG.

Brázdil et al. (2005) recorded intracerebral ERPs during a two-stimulus auditory oddball task in eight epileptic patients. Among the 606 intracerebral electrode sites investigated, only one was located in the insula, and although a “positive observation” was reported by the authors, there was no further information on the specific timing and location of this response. Clarke et al. (1999) reported a late, post-response, negative-going slow-wave component at insular/opercular electrode sites following rare targets in six patients, but no P3-like component during a visual oddball procedure.

However, insular contacts in their study appeared to be located exclusively in the pI. Boucher et al. (2015) did not find GBRs in the insular cortex to saliency information processing. However, their patients with insular contacts had the seizure focus localized in the insula. A recent iEEG-study has reported gamma-band oscillations (40-90 Hz) in the insula following thermo-nociceptive stimuli presentation (Liberati et al., 2017). The authors reported the role of the insula in the perceptual processing. However, no distinction between aI and pI in deeper attentional processing was investigated in the high-gamma frequency.

We observed P300 responses in both the left and the right insulae, with no obvious difference in latency and amplitude, as described in some neuroimaging studies (e.g., Linden et al., 1999). Other authors have previously showed a predominance of the right side for visual target-stimuli detection (e.g., Downar et al., 2000). Uddin (2015) proposed that an anomalous interaction between the right dorsal aI and other large-scale brain networks (i.e., the default-mode network and central executive network) could result in altered attentional processes, suggesting a key role of the right dorsal aI in salience processing. Our ERP results do not support such precedence for the right over the left insula in the attentional processes under study. Nevertheless, we cannot exclude the possibility that laterality-dependent effects would be observed in response to affective stimuli. Indeed, several lesion studies have highlighted the crucial participation of the right aI in the emotional processing (Phillips et al., 1997; Terasawa et al., 2015), and Paulus and colleagues (2003) have also showed a specific activation of the right aI following aversive stimuli presentation.

Out of six patients with electrode contacts in the aI, two (Pt's #5 and #8) did not show a significant P300 response. For one of them (Pt. #5), a left insular dysplasia was found on the MRI, and a left temporo-insular epileptic focus was identified, which might explain the lack of effect observed. This same patient was excluded from GBR analyses due to noise associated with inter-ictal high-

frequency activity. The other patient (Pt. #8) had a right frontal cortical dysplasia (type II) and, although the insula was not found to be involved in the epileptic seizure genesis, we cannot exclude some cortical reorganization affecting the insula due to the dysplasia (Burneo et al., 2004; Gondo et al., 2000). By contrast to ERP analyses, we recorded GBRs in all aI contacts during target detection for this patients (Pt. #8). These seemingly contradictory findings illustrate how ERP and GBR analyses may offer complementary information. Indeed, P300 ERP responses mostly reflect theta and delta frequency activities (Bernat et al., 2007; Kolev et al., 1997).

In one patient (Pt. #6), the P3b recorded in the three aI contacts for target stimuli differed from the standard stimuli but did not differ significantly from the novel stimuli. This may be attributable to the low number of novel trials for these three contacts (21%) kept for analysis after artifact rejection compared to target stimuli (53%) in this subject (significant statistical comparison (t (3) = -11.58, p = 0.007), thereby affecting statistical power for target vs. novel stimuli in this patient. We did not find aI contacts with P300 activity in response to novel stimuli in comparison to standard stimuli, and only 3/15 aI contacts showed GBRs for this comparison. Thus, the aI does not seem to respond preferentially to rare stimuli, but rather to task-relevant stimuli, suggesting a top-down effect related to attentional control (Clark et al., 2000; Nelson et al., 2010). The aI plays a major role in affective processing including emotional evaluation, social cognition, empathy and consciousness emotional (e.g., Berntson et al., 2011). Furthermore, Menon and Uddin (2010) have proposed that the aI would help to integrate bottom-up salient information in initiating attentional control signal. As the stimuli involved in our task were emotionally neutral, we cannot exclude the possibility that the aI is involved in bottom-up detection of task irrelevant, but emotionally relevant novel stimuli (Britton et al., 2006; Phan et al., 2004; Zhang et al., 2018).

One patient (Pt. #2) showed significant P300 responses in the pI for target-stimuli detection around 326 ms post-stimuli, which was not seen in the other participants. Although these inter-individual differences may be attributable to differences in the specific locations of the insular contacts or to the fact that contacts may not have all been implanted in the same cortical layer, this may also reflect inter-individual differences in anatomo-functional organization of the insular cortex, possibly due to plasticity (Scharfman, 2002). This patient also showed GBRs in the pI for target stimuli in comparison to novel and standard stimuli around 400-600 ms post-stimuli.

Together, ERP and GBRs results for the aI contacts showed that this insular subportion is involved in top-down attentional processing. Contrary to our expectations, several pI contacts showed a later target-dependent modulation of GBRs in comparison to novel and standard stimuli presentation. Rather than indexing attentional processing, this activity may reflect somatosensory or motor responses associated with target responding, which would be congruent with the role of the pI in sensorimotor processing (Cauda et al., 2011; Kishima et al., 2007; Nguyen et al., 2009). This hypothesis is supported by the fact that pI contacts showing these relatively late GBRs were all localized in the left hemisphere, while all participants pressed the response button using the right hand. Future studies using similar paradigms should use non-motor responses (e.g., counting the targets) to rule out the possibility that the recorded pI activity is attributable to such processes.

This study is limited by factors that are inherent to iEEG studies with epileptic patients. These include the incomplete coverage of the insular cortex by intracranial electrodes, the limitation of generalization of our results due to the possible influence of epilepsy (especially in the three patients for whom the epileptic focus involved in insula) and cortical dysplasia on the functional organization of the insula, and the influence of medication on neural activity. Despite these limitations, our results are congruent across patients as well as with prior studies with healthy participants.

This study examined attentional processes in the insular cortex through direct intracranial EEG recordings by exploring ERP subcomponents and GBRs obtained during a three-stimulus visual oddball task. Our findings suggest that visual target detection is associated with a P300 response in the aI which seems to correspond to the P3b component seen in scalp-EEG studies, underlying voluntary attentional processing. This P300 response appeared to be independent from the hemisphere where recordings were obtained and was not consistently observed in the pI. GBRs were also recorded in response to target stimuli, occurring earlier in the aI (from ≈200-300 ms) then in the pI (from ≈400-500 ms). This temporal separation might reflect contribution of the aI to voluntary attentional processing, and the role of the pI in sensorimotor processing.

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ARTICLE II

SPATIOTEMPORAL DYNAMICS OF AUDITORY INFORMATION PROCESSING IN THE INSULAR CORTEX: AN INTRACRANIAL EEG STUDY USING AN ODDBALL PARADIGM.

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Abstract

Functional neuroimaging studies using auditory stimuli consistently show activation of the insular cortex. However, due to the limited temporal resolution of non-invasive neuroimaging techniques, the role(s) of the insula in auditory processing remains unclear. As the anterior insula (aI) and the posterior insula (pI) have different connections and are thought to be functionally distinct, it is likely that these two areas contribute differently to auditory processing. Our study examines the spatiotemporal dynamics of auditory processing in the insula using intracranial electroencephalography (EEG). Eight epileptic patients completed two passive listening tasks and one three-stimulus auditory oddball detection task during the intracranial EEG monitoring of their drug-resistant seizures. Recordings were obtained from depth electrodes implanted in 11 insulae. Event-related potentials (ERPs) were analyzed using permutation analyses during the N100 and the P300 intervals, and modulations of alpha, theta and gamma band responses were compared using Wilcoxon/Mann-Whitney analyses. N100 responses to auditory stimuli were mostly observed in the pI and were little affected by task conditions. Auditory target detection was associated with P300 ERPs, and alpha, theta, high- and low-gamma responses, preferentially at aI contacts. Results suggest that the aI is involved in voluntary attentional processing of task-relevant information, whereas the pI is involved in automatic auditory processing.

Short running title: Insular auditory processing

Keywords: Attention; Epilepsy; Insula; intracranial EEG; Salience network

Introduction

The insular cortex is a paralimbic structure located deep in the Sylvian fissure, hidden behind the frontal, temporal, and parietal opercula. The central insular sulcus separates the anterior insula (aI), comprising the anterior, middle, and posterior short insular gyri, from the posterior insula (pI), which is composed of the anterior and posterior long insular gyri (Flynn 1999; Ture et al. 1999). The insula has been associated with multiple functions, including autonomic and vestibular functions, interoception, sensory functions (visceral, somatosensory, auditory, gustatory, and olfactory), affective (emotions and empathy) and cognitive (language, attention, decision-making, memory) processing (Oppenheimer et al. 1992; Craig 2003; Nagai et al. 2010; Mazzola et al. 2014; Avery et al. 2015; Uddin et al. 2017). Several studies have revealed a functional differentiation within the insular cortex, the pI being activated by sensory and chemosensory stimuli, while the aI is activated during cognitive and attentional tasks; the latter also plays a critical role in the "salience network" (Kurth et al. 2010; Menon and Uddin 2010). However, its specific involvement in attentional processing remains unclear in part due to the rare prevalence of damage restricted to the insula, limiting lesion-symptom mapping (Cereda et al. 2002).

Previous studies suggest an important role of the insula in auditory processing (Bamiou et al. 2003). This is not surprising considering its wide afferent and efferent connections with auditory areas (e.g., superior temporal gyrus, medial geniculate body of the thalamus, temporal pole and auditory temporal areas) (Jones and Burton 1976; Augustine 1996; Flynn 1999; Ghaziri et al. 2017; Mulert et al. 2004). Lesions studies have reported several auditory impairments following insular damage, and these include auditory agnosia to environmental sounds (Spreen et al. 1965; Habib et al. 1995), speech sound identification (Hyman and Tranel 1989; Fifer 1993), and altered emotional perception and

experience when listening to music (Peretz et al. 1994; Habib et al. 1995; Ayotte et al. 2000; Griffiths et al. 2004). Deficits in temporal resolution and sequencing (Bamiou et al. 2006) and hyperacusis have also been reported (Tomasino et al. 2014; Boucher et al. 2015b). The role of the insula in auditory processing is further supported by electrocortical stimulation studies which showed auditory disturbances (e.g., distant sounds, buzzing, whistling, illusion, and hallucination symptoms, and a feeling of hearing things in echo) in response to pI stimulation (Isnard et al. 2004; Nguyen et al. 2009; Afif et al. 2010; Pugnaghi et al. 2011). Despite this accumulating evidence, the specific role of the insula in auditory processing and whether this role differs according to insular subregions remain unclear.

Functional neuroimaging studies have provided evidence that the aI region is involved in general and controlled attentional processing (Dosenbach et al. 2006; Dosenbach et al. 2008; Nelson et al. 2010). More specifically, it has been suggested that the aI is involved in a "target detection network," along with the supramarginal gyrus, the frontal operculum, the superior parietal lobule, and the anterior cingulate cortex (Clark et al. 2000; Ardekani et al. 2002). Recently, the aI has been placed in the core of the "salience network model" together with the anterior cingulate cortex, subcortical, and limbic structures (Menon and Uddin 2010; Uddin 2015).

Several neuroimaging studies have reported an aI activation in response to multimodal target detection, highlighting the role of the aI in identifying the salient stimuli to mediate attentional processing (Linden et al. 1999; Clark et al. 2000; Downar et al. 2000; Stevens et al. 2000; Kiehl et al. 2001; Nelson et al. 2010; Chen et al. 2015). Positron emission tomography has demonstrated aI responses during passive sound listening (Engelien et al. 1995). Using an auditory target detection task in an event-related fMRI study, Kiehl and colleagues (Kiehl et al. 2001) reported a bilateral activation of the insula for both target and novel auditory stimuli, with a greater response for target-

tone, reflecting voluntary attentional processing. Several studies have also reported a crucial role of the insula for salient stimuli such as emotional music (Koelsch et al. 2018). Furthermore, the insula is activated during both temporal and spatial detection tasks using auditory stimuli (Rao et al. 2001; Pastor et al. 2006; Kosillo and Smith 2010). Currently, the contribution of each portion of the insula to auditory information processing remains unclear, which is partly attributable to the limited temporal resolution of neuroimaging techniques.

Electroencephalography (EEG) allows the characterization of the time course of sensory and cognitive processes following multimodal stimulus presentation, and can dissociate endogenous (i.e., bottom-up) from exogenous (i.e., top-down) mechanisms. The event-related brain potential (ERP) N100 (or N1) is typically observed after any auditory stimulus presented in a passive auditory task, and is thought to reflect an early automatic attentional processing (i.e., bottom-up) indexed by a negative-amplitude component peaking around 50 – 150 ms post-stimulus (Näätänen and Picton 1987). Large intracerebral sources are involved in N100 genesis, including the fronto-central area, superior temporal sulcus, temporo-parietal cortex, and auditory cortex on the supratemporal plane (Näätänen and Picton 1987; Woods 1995; Picton et al. 1999; Tiitinen et al. 1999). Another ERP component, the P300 (or P3b), is recorded at centro-parietal scalp electrodes following the detection of an unpredictable target stimulus. This positive-amplitude component peaking around 300-500 ms post-stimulus is thought to reflect voluntary and controlled (i.e., top-down) attentional processes. Generally, the P3b component, elicited by a relevant stimulus, is distinguished from the P3a component, which occurs 225 – 300 ms post-stimulus for a novel task-irrelevant stimulus and is associated with an involuntary attentional processing, such as the orienting response (i.e., bottom-up) (Squires et al. 1975; Snyder and Hillyard 1976; Posner et al. 1980; Donchin et al. 1988; Polich and Kok 1995; Comerchero and Polich 1999; Friedman et al. 2001; Ardekani et al. 2002; Polich 2007).

Electrophysiological studies have used low-resolution electromagnetic tomography (LORETA) and combined EEG-fMRI studies to identify the cortical sources of the P3 subcomponents recorded during an oddball detection paradigm. These studies suggest that the neural generators of the P3a are localized in cingulate region, inferior frontal gyrus, insula, inferior parietal lobule and right parietal areas (Linden et al. 1999; Clark et al. 2000; Ranganath and Rainer 2003; Bledowski et al. 2004a; Bledowski et al. 2004b; Linden 2005), whereas the P3b generators include inferior and middle frontal gyrus, superior and inferior parietal lobules, limbic regions, insula, anterior cingulate cortex, dorsolateral prefrontal cortex and superior temporal cortex (Linden et al. 1999; Clark et al. 2000; Bledowski et al. 2004a; Bledowski et al. 2004b; Mulert et al. 2004; Linden 2005; Volpe et al. 2007). Intracerebral ERP measurements in epileptic patients have shown that P3-like ERP responses to deviant visual and auditory stimuli were located along cingulate gyrus, inferior frontal sulcus, temporo-parietal and inferior temporal cortex, hippocampus and posterior parahippocampus (Baudena et al. 1995; Halgren et al. 1995a; Halgren et al. 1995b; Halgren et al. 1998; Velasco et al. 1986). In an intracranial EEG study with auditory stimuli, Alain et al. (1989) reported that potentials evoked by novel stimuli had shorter latencies than those evoked by target stimuli. Generators were located in the frontal, temporal, and parietal lobes.

Beyond ERP analysis, oscillatory characteristics of activity may provide additional information to understand sensory, affective, attentional, and cognitive processes (Fell et al. 2004; Mormann et al. 2005; Hanslmayr et al. 2007). Several studies have shown an increased high-gamma frequency activity (> 40 Hz) during a variety of sensory and cognitive functional activities (Jensen et al. 2007; Ray et al. 2008; Lachaux et al. 2012). More specifically, gamma-band responses have been associated with multiple aspects of auditory processing, including passive sound discrimination, directed attentional tasks, and auditory selective attention (Crone et al. 2001; Jensen et al. 2007; Kaiser et al. 2002;

Edwards et al. 2005). Debener and colleagues (Debener et al. 2003) have reported gamma-band responses (40 Hz) following target stimulus presentation, highlighting the involvement of gamma frequency in goal-directed processing rather than in stimuli-driven processing (i.e., novel stimuli). On the other hand, in the time interval of the mismatch negativity wave (i.e., around 50 ms post-stimulus), Marshall et al. (1996) have reported that the gamma activity was more strongly increased for the auditory deviant stimulus compared to standard stimulus presentation. Other studies have reported an increased gamma response at 80 ms after stimulus onset, followed by a gamma decrease response in the time window of the P3 wave, reflecting a different generation of gamma activity between pre-attentive and attentive auditory stimuli processing (Crone et al. 2001; Fell et al. 2003, 2004; Jensen et al. 2007; Marshall et al. 1996). Several studies have also reported that low frequency oscillatory synchrony may be enhanced by attentional processing (Crone et al. 2001; Sauseng et al. 2006; Womelsdorf and Fries 2007; Schroeder and Lakatos 2009). Numerous studies have reported that alpha band oscillations (8-12 Hz) have an inhibitory function reflected by a decrease in alpha modulation for task-engaged regions, while alpha power increases in task-irrelevant regions (Bonnefond and Jensen 2015; Foxe and Snyder 2011; Jensen and Mazaheri 2010; Klimesch et al. 2012). Strauss and colleagues (2014) have reported that alpha frequency was preponderant in the inhibition of auditory noise to improve auditory selective attention in task-relevant regions. Other studies have reported that low-frequency activities, as theta band (4-7 Hz), was related to active discrimination processing (Demiralp and Basar 1992; Schürmann and Basar 1994; Yordanova and Kolev 1998). In an auditory oddball task, Ko and colleagues (2012) have reported early theta oscillations following deviant and standard stimulus presentation, whereas at around 250 ms post-stimuli, theta activity was only related to deviant stimuli presentation.

In the past decade, it has been demonstrated that a non-negligible proportion of surgical candidates with drug-resistant epilepsy have seizure focus involving the insula (Isnard et al. 2004; Nguyen et al. 2009; Obaid et al. 2017). Because the insula is located in the depths of the Sylvian fissure and in proximity to other potential epileptic areas, invasive intracranial EEG (iEEG) recordings are often necessary to confirm an epileptic focus that involves the insular cortex (Surbeck et al. 2011). Such recordings provide an unprecedented opportunity to study the role of the insular cortex by combining the excellent spatial resolution of fMRI with the high temporal resolution of EEG (Lachaux et al. 2003). The present study aims to characterize the spatiotemporal dynamics of auditory information processing in the insula using iEEG.

Materials and methods

Participants

Participants were eight epileptic patients (four women; mean age: 29.8 yrs, range 18 – 44; all right-handed) undergoing invasive iEEG as part of a pre-surgical evaluation for their drug-resistant seizures to better define the epileptogenic zone. All participants had previously undergone a comprehensive neuropsychological assessment as part as the presurgical monitoring of their drug-refractory seizures, and none had intellectual disability or severe attentional, language, or memory problems that could interfere with the administration of the auditory tasks used in the present study. The characteristics of the study participants are summarized in Table 1. A total of 62 electrode contacts were implanted in 11 insulae (5 right, 6 left). The study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki and was approved by the CHUM ethics committee.

Tableau 1. – Descriptive characteristics of the study participants

Pt. #	Gender	Age (yrs)	Age at 1st seizure (yrs)	Extra insular SEEG recorded areas	Total no. of recording contacts	No. of contacts for analysis	No. of contacts in the insula	Pre-surgical cerebral MRI findings	Seizure focus
1	F	18	10	L (F, P, T)	116	113	6 (6 L aI)	Amygdalectomy	L Anterior insula
2	M	22	10	L (P, T)	110	110	3 (3 L pI)	Normal	Unclear (possibly L temporal)
3	M	23	11	L (F, T) and R (F, T)	113	101	11 (2 L aI; 1 R aI; 4 L pI; 4 R pI)	Normal	Bitemporal (Hippocampus)
4	M	27	22	R (OF, C) and L (OF, C)	144	143	8 (8 R aI)	Normal	Unclear (possibly L posterior cingulate)
5	F	32	30	L (F, T, P, O)	116	111	10 (6 L aI; 4 L pI)	Normal	L temporo-insular
6	F	37	23	L (C, F, P) and R (C, F, P)	101	95	19 (3 L aI; 3 R aI; 7 L pI; 6 R pI)	Left insular dysplasia	R Cingular cortex
7	F	35	21	R (F, T)	84	82	2 (2 R pI)	Normal	R Operculo-orbito-insular
8	M	44	12	R (F, T)	94	92	3 (3 R aI)	Right frontal cortical dysplasia (type II)	R Middle and inferior frontal gyri junction

Abbreviations. R, right; L, left; F, frontal; I, insula; P, parietal, O, occipital; T, temporal; C, cingulate; OF, orbitofrontal, aI, anterior insula; pI, posterior insula

Auditory tasks

Three auditory tasks were administered to examine sensory and attentional processes in the insular cortex. Patients were tested in their hospital room at least three days after intracranial electrodes implantation. Auditory stimuli were first calibrated using a digital sound level meter (RadioShack 33-2055) to ensure the intensity of tones. Each frequency tone (i.e., 500 Hz, 1,000 Hz, 2,000 Hz and 4,000 Hz) was tested at 55, 60, 75 and 90 dB intensities.

A first task (frequency task) was administered in order to ensure that the insular response to auditory tones is not modulated by auditory frequency (Hz). Tones of four different frequencies (500 Hz, 1,000 Hz, 2,000 Hz, and 4,000 Hz; 25% probability for each frequency) were presented binaurally over ear inserts (3M™ E-A-RLINK™ Auditory Systems) while the participant was instructed to watch a silent movie, without paying attention to sounds. The Intensity of the sound was 60 dB, with 50 ms duration, a 5 ms rise/fall time, and an inter-stimulus interval of 2,000 ms. One block contained 75 stimuli for each of the four frequencies. The total task included two blocks for a total of 600 stimuli presented in a pseudorandomized order.

In the second task (passive auditory oddball), three different auditory stimuli [i.e., standard (1,000 Hz-tone, 70% probability), deviant-low frequency (500 Hz-tone, 15% probability), and deviant-high frequency (2,000 Hz-tone, 15% probability) stimuli)] were presented while the patient was watching a silent movie. The intensity of stimuli was 70 dB, with 50 ms duration, a 5 ms rise/fall time, and an inter-stimulus interval of 2,000 ms. The total task included six blocks of 100 stimuli presented in a pseudorandomized order.

The third task (active auditory oddball) was exactly the same as the passive auditory oddball task described above, except that the patient was instructed to fix a point on the computer screen and to press the spacebar on the keyboard with their right index finger as quickly as possible to the

deviant-high-frequency (target) stimulus, and to ignore standard and deviant-low-frequency (novel) stimuli. All tasks were implemented in Presentation Software (neurobehavioral system: http://www.neurobs.com).

IEEG recording and analyses

EEG acquisition was performed at 2 kHz using a Stellate Harmonie audio-video-EEG monitoring system (Natus Medical, San Carlos, CA) by means of grid electrodes, subdural grids and depth electrodes (Ad-tech medical instruments, Racine, WI). Insular depth electrode contacts had a diameter of 1.1 mm, a length of 2.3 mm, and were spaced 5 mm apart from center to center. One mastoid was used as ground and the other as reference. For localization of electrode contacts, a 3D reconstruction with Stellate Gridview software was performed on postimplantation MRIs for each patient. Stellate Gridview coordinates were transformed to Talairach coordinates to allow an automatic localization of contacts according to the Talairach Daemon atlas (Lancaster et al. 2000). A total of 62 contacts in the insula were analyzed in the present study.

Electrophysiological data were processed using Brain Vision Analyzer 2.0.1 software (Brain Products, Munich, Germany). For each participant, data were re-referenced to the average of all intracranial electrode contacts, except those with artefacts in the whole signal (31/878, 3.5%, see Table 1). All signals were down-sampled off-line to 500 Hz. Automatic artefact rejection (± 300 µV) and manual inspection of the data were performed to remove epileptic activity and epochs containing noise. For the active oddball task, trials with errors or with a response occurring before 200 or after 2,000 ms post-target stimulus were excluded from the analysis.

ERP analysis

The EEG signal was segmented from -200 to 1,000 ms post-stimulus onset, separately for each task condition (i.e., target, novel, and standard). A baseline correction was applied -200 ms pre-stimulus. High and low pass filters were set at 0.1 and 30 Hz (Demiralp et al. 2001) and we applied a notch filter at 60 Hz, as suggested by Guger (Guger et al. 2011). Digital filtering was applied on the continuous data before creating epochs. Automatic peak detection was used to measure amplitudes and latencies relative to stimulus onset. The N100 was defined as the most negative point between 50 and 150 ms (N100), whereas the P300 was defined as the most positive point between 225 and 400 ms (P300) post-stimulus. Percentages of kept trials per insula were similar across conditions, for all three tasks (see Supplemental Table S1). Analyses were performed using Brain Vision Analyzer 2.0.1 software.

Time-frequency analysis

Data were segmented from -500 to 1,500 ms post-stimulus onset (low-gamma and high-gamma bands) and from -1250 to 1750 ms post-stimulus onset (theta and alpha bands), separately for each condition of oddball tasks (i.e., target, novel, and standard), and each condition of the frequency task (i.e., 500 Hz, 1,000 Hz, 2,000 Hz, and 4,000 Hz). We performed continuous time-frequency analysis over each trial using complex Gaussian Morlet's wavelet in high frequency range of 70-150 Hz (high-gamma frequency; eight separate 10 Hz linear steps with a Morlet parameter set at 7), in frequency range of 30-50 Hz (low gamma frequency; six separate 3.3 Hz linear steps with a Morlet parameter set at 6), in frequency range of 4-7 Hz (theta frequency; three separate 1 Hz linear steps with a Morlet parameter set at 3), and in frequency range of 8-12 Hz (alpha frequency; four separate 1 Hz steps with a Morlet parameter set at 4). A relative normalization (i.e., baseline correction) was applied from -200 to -50 ms for low- and high-gamma frequency bands and from -500

to -50 ms for theta and alpha frequency bands. In addition, for low- and high-gamma frequency bands, we used a normalization method described by Boucher and colleagues (Boucher et al. 2015a) for correction of the power decrease of the signal with increasing frequency, since event-related high-gamma band responses are broadband (Lachaux et al. 2012). For each gamma frequency layers, the power value for a given time interval was divided by the median value, on the same frequency band, from all the pre-stimulus baseline epochs [i.e., median value calculated on the three (i.e., oddball tasks) and on the four (i.e., frequency task) pre-stimuli conditions]. Broadband activity was computed by calculating the average of all normalized frequency layers of the low- and high-gamma frequencies. For all frequencies, epochs with outliers value (>3.29 S.D. from the mean) were excluded. This procedure was repeated for each time interval, including the baseline (-500 or -200 to -50 ms) and for each 100-ms intervals from 0 to 1,000 ms post-stimulus. The values obtained represent the mean broadband high-gamma, low gamma, alpha, and theta power over a time interval of 100 ms duration, expressed as the percentage of power change relative to baseline level for each insular contact. These procedures were performed using MatLab software (R2015a). Evoked responses were not subtracted in our time-frequency analyses.

Statistical analyses

ERPs analysis

Nonparametric permutations were performed (1,000 permutations) using MatLab software (R2015a) (see Galan et al. 1997). For each task, we first identified electrode contacts showing significant ($p < 0.01$) activity in the 50-150 ms and 225-400 ms intervals in comparison to baseline, in any condition [i.e., frequency task: 500 Hz, 1,000 Hz, 2,000 Hz, and 4,000 Hz; oddball tasks: standard (except for P300 analyses), target, and novel stimuli], using paired *t* tests. Then, for each contact

identified at the first step, independent t-tests were performed to test for amplitude differences across conditions, during the time interval selected ($p < 0.05$). ERP analyses were carried out for each time point in these two time intervals. For each task, we applied a Bonferroni correction to correct for multiple comparisons by dividing the alpha value criterion by the number of comparisons. Thus, differences between conditions were considered statistically significant at $p < 0.008$ for the frequency task, and at $p < 0.017$ for the oddball tasks.

Time-frequency analysis

For the frequency task, the electrode contacts showing significant ($p < 0.05$) responses in high- and low-gamma, alpha, and theta frequency bands associated with stimulus presentation of 500 Hz, 1,000 Hz, 2,000 Hz and 4,000 Hz were identified to compare frequency powers (i.e., mean value of layers for each condition, within each frequency band) during each post-stimulus 50 ms time interval to that of the pre-stimulus baseline epoch (-500 or -200 to -50 ms) on the same contact, using Wilcoxon signed-rank tests. Then, due to the number of comparisons between conditions in this task (i.e., 500-1,000 Hz, 500-2,000 Hz, 500-4,000 Hz, 1,000-2,000 Hz, 1,000-4,000 Hz, 2,000-4,000 Hz), we conducted a one-way analysis of variance (ANOVA) with condition as the four level-factor and multiple comparisons with a Bonferroni correction with a $p < 0.01$ criterion, for significant differences. Four different one-way ANOVAs were conducted, for each frequency band separately.

For the oddball tasks, we used as previously the Wilcoxon signed-rank test to identify electrode contacts showing significant ($p < 0.05$) difference on frequency powers associated with target and novel conditions (i.e., mean value of layers for each condition) during each post-stimulus 25 ms time interval to that of the pre-stimulus baseline epoch (-500 or -200 to -50 ms) on the same contact, in alpha, theta, high- and low-gamma frequency bands. Then, a mixed-ANOVA model was conducted on the frequency powers in time intervals of 50-150 ms and of 250-600 ms post-stimuli,

with regions (aI vs. pI) and laterality (left vs. right) as between-factors and, with condition (target, novel, and standard) as within-factor. We did not consider the different number of electrode contacts across patients, and thus significant contacts in the same insular portion and laterality were averaged for each patient. A second mixed-ANOVA was conducted without the laterality factor. Bonferroni correction was applied for multiple comparisons with a $p < 0.01$ criterion for significant differences. Mixed ANOVAs were conducted across oddball tasks (active and passive) in two time intervals (50-150 ms vs. 250-600 ms), and for the four frequency bands.

Individual electrode contacts were analyzed separately for each patient, in both oddball tasks. Electrode contacts showing a significant response ($p < 0.05$) in high- and low-gamma, alpha, and theta frequency bands associated with presentation of target and/or novel stimuli were identified using Wilcoxon signed-rank tests. Then, for each difference significant on frequency powers identified (i.e., each poststimulus 25 ms time interval different from its baseline at the same contact), Mann-Whitney nonparametric tests were conducted to compare frequency responses with each pair of condition (i.e., target vs. standard; novel vs. standard; target vs. novel). At this step, a $p < 0.017$ criterion was used for each contact. All analyses were conducted in Matlab software (R2015a).

Results

Behavioral results

Table 2 summarizes the performance of each participant on the active oddball task. On average, the task was well executed by all patients. With the exception of Pt #7, who made a considerable number of errors, all patients detected > 75% of targets and made few (< 10%) false alarms on non-target trials. Pt #7 was thus excluded in analyses involving the active oddball task. Mean reaction time differed strongly across participants.

Tableau 2. – Behavioral results on the active auditory oddball task

Pt. #	% Hits	% False alarms	Mean ± SD Hit RT (ms)
1	81.0	0.0 %	638 ± 104
2	81.0	3.9 %	563 ± 127
3	91.0	1.1 %	578 ± 134
4	100.0	0.0 %	560 ± 161
5	86.0	6.0 %	401 ± 54
6	76.7	0.0 %	620 ± 127
7	47.0	33.0 %	519 ± 377
8	97.0	0.0 %	518 ± 117

IEEG results

Frequency task

Pt # 8 was excluded of this analysis because of noise contaminating data in the whole iEEG signal. ERP analyses revealed that 7/32 (21%; all in Pt. #4) of aI contacts showed a significant amplitude difference in the N100 interval in comparison to baseline, and this N100 deflection was observed independently of the tone frequency (i.e., 500, 1,000, 2,000, and 4,000 Hz). Mean N100 latency in these aI contacts was at 92 ms post-stimulus. By contrast, a N100 deflection was recorded at 24/30 (80%) of pI contacts: 19/30 (63%) for 500-Hz tones, 24/30 (80%) for 1,000-Hz and 2,000-Hz tones, and 23/30 (77%) for 4,000-Hz tones compared to baseline. Weighted-average N100 peak latency in the pI was 89 ms post-stimulus. These responses were recorded in both the left (15/18, 83%) and the right (9/12, 75%) hemispheres. Although amplitude differences were occasionally observed across conditions, there was no clear pattern suggesting greater (or smaller) amplitude for any specific conditions (data not elaborated). ERP analyses showed no significant P300 deflection for any of these tones. Although one-way ANOVAs occasionally showed a main effect of the condition factor in the four frequency bands, multiple comparisons analyses showed no clear different frequency powers between conditions (data not elaborated).

Passive oddball task

ERP analyses

ERP analyses revealed that 6/32 (19%; all in Pt. #4) of aI contacts showed a significant amplitude difference in the N100 interval in comparison to baseline, and this N100 deflection was observed for each task condition (i.e., standard, deviant-low frequency, deviant-high frequency; see Table 3). Mean N100 latency in these aI contacts was at 90 ms post-stimulus. Among pI contacts, 25/30 (83%) displayed a N100 response following deviant-high-frequency (24/30, 80%), deviant-low-frequency (18/30, 60%), and standard (24/30, 80%) stimuli in comparison to baseline. Comparisons between conditions revealed greater amplitudes for standard stimuli than for deviant-low frequency (9/24; 38%) and for deviant-high frequency (4/24; 17%) at some electrodes, but the opposite pattern was found (deviant-high > standard: 9/24; 38%; deviant low < standard: 3/18; 17%) at others. N100 amplitude was larger for deviant-high frequency stimuli than for deviant-low stimuli for 10/24 (42%) contacts, and the opposite pattern was not found for any contact. These responses were recorded in both the left (15/18, 83%) and the right (10/12, 83%) hemispheres. Weighted-average (i.e., after averaging significant contacts of each patient) N100 latency in the pI was at 93 ms post-stimulus. The distribution of insular contacts showing a N100 response following auditory stimuli in the passive oddball task is shown in Figure 1. We did not observe a significant P300 response at any insular contact during the passive oddball task.

Figure 1. – Distribution of the insular electrode contacts showing a significant N100 deflection in response to (any) auditory stimulus presentation during the passive oddball task (blue). Contacts not significant are in white color.

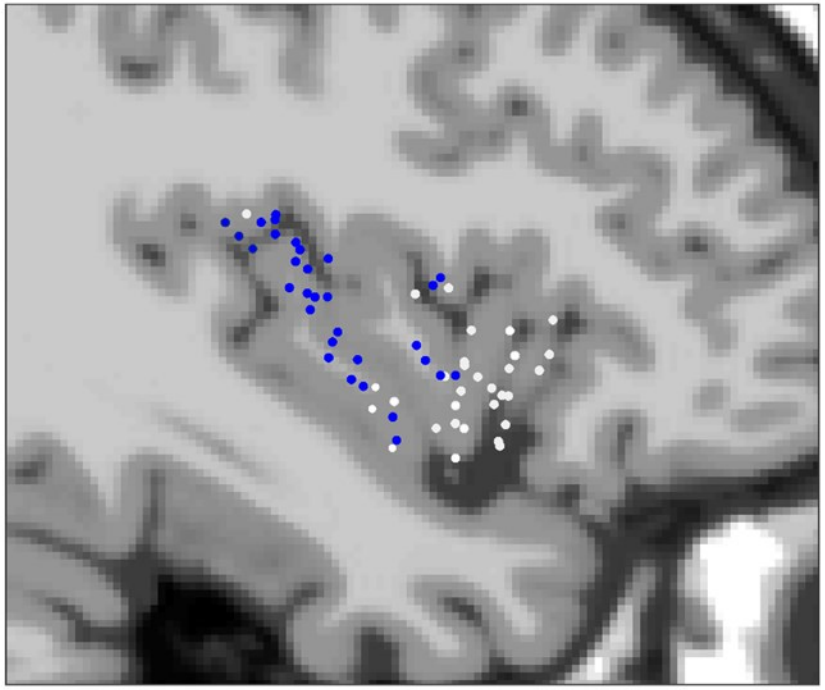


Tableau 3. – N100 (50-150 ms) responses to target, novel, and standard stimuli during the passive auditory oddball task

Pt. #	Anterior insula						Posterior insula					
	Contact	Hemisphere	Gyrus	N100 latency	N100 amplitude	Comparison	Contact	Hemisphere	Gyrus	N100 latency	N100 amplitude	Comparison
1	u11	Left	as-aps	-	-	-						
	u12	Left	as	-	-	-						
	u13	Left	as	-	-	-						
	u31	Left	as	-	-	-						
	u32	Left	as	-	-	-						
	u52	Left	as	-	-	-						
2							u32	Left	al	N (148 ms) S (54 ms) T (60 ms)	-4.91 µV -14.99 µV -7.03 µV	S>T; S>N
							u33	Left	al	N (56 ms) S (64 ms) T (62 ms)	-20.85 µV -28.80 µV -18.16 µV	S>N; S>T; T>N
							u34	Left	al	N (58 ms) S (66 ms) T (108 ms)	-7.50 µV -16.86 µV -9.45 µV	S>T; S>N; T>N
3	u11	Left	as-ia	-	-	-	u31	Left	pcs	S (112 ms) T (106 ms)	-5.90 µV -14.87 µV	T>S
	u12	Left	as	-	-	-	u32	Left	pcs	N (112 ms) S (102 ms) T (98 ms)	-20.33 µV -20.36 µV -26.42 µV	N>S
	u21	Right	as-ms	-	-	-	u33	Left	al	N (108 ms) S (90 ms) T (92 ms)	-14.90 µV -20.03 µV -33.23 µV	T>S; N>S; T>N
							u34	Left	al	N (88 ms) S (82 ms)	-22.87 µV -28.53 µV	T>S; T>N

										T (84 ms)	-36.02 µV	
							u41	Right	al	-	-	-
							u42	Right	al	S (104 ms)	-17.06 µV	-
										T (106 ms)	-18.16 µV	
							u43	Right	al	N (110 ms)	-18.15 µV	T>S
										S (102 ms)	-20.76 µV	
										T (102 ms)	-33.41 µV	
							u44	Right	al	N (86 ms)	-36.61 µV	N>S
										S (82 ms)	-29.05 µV	
										T (86 ms)	-33.52 µV	
4	u11	Left	ms	-	-	-						
	u12	Left	ms	-	-	-						
	u13	left	ms	S (88 ms)	-4.47 µV	-						
	u14	Left	ms	N (84 ms)	-3.15 µV	-						
				T (88 ms)	-6.03 µV							
				S (88 ms)	-5.59 µV							
	u15	Left	ms	N (86 ms)	-4.85 µV	-						
				T (86 ms)	-4.23 µV							
				S (90 ms)	-4.97 µV							
	u21	Right	ms	N (98 ms)	-5.00 µV	-						
				S (88 ms)	-5.00 µV							
	u22	Right	ms	N (96 ms)	-3.99 µV	-						
				T (92 ms)	-3.55 µV							
				S (88 ms)	-5.02 µV							
	u23	Right	ms	T (92 ms)	-3.35 µV	-						
				S (90 ms)	-3.29 µV							
5	u13	Left	as	-	-	-	u31	Left	al	-	-	-
	u14	Left	as	-	-	-	u32	Left	al	S (128 ms)	-16.43 µV	-
	u16	Left	as	-	-	-	u33	Left	al	S (138 ms)	-10.25 µV	-
										T (134 ms)	-23.62 µV	

	u17	Left	as	-	-	-	u34	Left	pl	T (120 ms)	-20.72 µV	-
	u35	Left	ms	-	-	-						
	u36	Left	as	-	-	-						
6	u11	Left	sis	-	-	-	u31	Left	cs	-	-	-
	u12	Left	ms-sis	-	-	-	u32	Left	cs-li	-	-	-
	u13	Left	ms-sis	-	-	-	u33	Left	al	T (106 ms)	-17.88 µV	-
										S (112 ms)	-11.91 µV	
	u21	Right	as-ia	-	-	-	u34	Left	al	T (100 ms)	-25.37 µV	T>S
										S (98 ms)	-14.42 µV	
	u22	Right	ms-sis	-	-	-	u35	Left	al	T (96 ms)	-28.04 µV	T>N
										N (108 ms)	-17.18 µV	
										S (96 ms)	-20.45 µV	
	u23	Right	ms-sis	-	-	-	u36	Left	al	T (92 ms)	-34.73 µV	T>N; T>S
										N (102 ms)	-8.78 µV	
										S (92 ms)	-23.16 µV	
							u37	Left	al	T (86 ms)	-42.06 µV	T>N; T>S
										N (64 ms)	-16.97 µV	
										S (84 ms)	-30.24 µV	
							u41	Right	al	T (92 ms)	-33.65 µV	T>S; S>N; T>N
										N (96 ms)	-9.83 µV	
										S (94 ms)	-22.16 µV	
							u42	Right	al	T (90 ms)	-39.78 µV	T>S; S>N; T>N
										N (92 ms)	-21.48 µV	
										S (94 ms)	-34.60 µV	
							u43	Right	al	T (82 ms)	-40.01 µV	S>N
										N (82 ms)	-28.59 µV	
										S (90 ms)	-38.12 µV	
							u44	Right	al	T (82 ms)	-48.91 µV	S>N; T>N
										N (82 ms)	-38.80 µV	
										S (84 ms)	-46.40 µV	
							u45	Right	al	T (82 ms)	-30.63 µV	S>N
										N (86 ms)	-26.24 µV	
										S (88 ms)	-29.65 µV	
							u46	Right	al	T (82 ms)	-12.47 µV	-
										N (88 ms)	-12.64 µV	
										S (88 ms)	-12.92 µV	

7							u41	Right	al	-	-	-
							u42	Right	al	N (132 ms) T (132 ms) S (126 ms)	-16.65 µV -28.01 µV -33.10 µV	S>N; T>N
8	u22	Right	as	-	-	-						
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						

Abbreviations. T = Target; S = Standard; N = Novel; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the N100 interval in comparison to baseline are identified with a '-'sign.

Conditions were only compared when waveforms showed significant post-stimulus activity in comparison to baseline.

All significant contacts showed a p-value < 0.01

Time-frequency analyses

There was no main effect of the laterality factor for any of the four frequency bands, and for any of the time intervals analyzed. Consequently, mixed ANOVAs without the laterality factor are reported in this section (Table 4; Figure 2). In the 50-150 ms time interval, analyses revealed significant main effects of condition and region, and a significant interaction between these factors, at all frequency bands. In the theta and alpha frequency bands, power increased for standard stimuli compared to deviant-high and deviant-low stimuli, whereas in low- and high-gamma frequency bands, power increased for deviant-high stimuli compared to standard and deviant-low stimuli, and increased for standard stimuli compared to deviant-low stimuli. Increases in theta, alpha, low- and high-gamma frequency power were significantly stronger at pI electrode contacts compared to aI contacts. In the 250-600 ms time interval, we observed no main nor interaction effect in any of the four frequency bands.

Nonparametric Mann-Whitney tests comparing each pair of conditions showed a significant theta modulation of an early and short-lasting (≈ 50-150 ms) response to standard stimuli compared to baseline for 9/30 (30%) of pI electrode contacts, and significant increased theta activity for standard stimulus compared to deviant-low stimuli for 9/9 (100%) of these contacts. Similar results were obtained in alpha frequency band (standard > baseline, 8/30 of pI contacts, 27%, and 8/8 of these contacts > deviant-low stimuli). High- and low-gamma modulations in an early and short-lasting (≈ 50-150 ms) response were observed in pI electrode contacts to deviant-high (3/30, 10%), standard (2/30, 7%), and deviant-low (1/30, 3%) stimuli compared to the baseline. Paired comparisons between these contacts were inconsistent (not elaborated). By contrast, only 2/30 (7%) of aI electrode contacts showed high- and low-gamma modulations to deviant-high stimuli relative to the baseline.

Figure 2. – All significant contacts for a given participant were averaged prior performing mixed-ANOVA. Each patient has the same weight in this analysis. Lines represent averages of theta, alpha, low- and high-gamma activities in aI (solid line) and pI (dotted line) for conditions (red: target, blue: novel and green: standard), in the passive task (left side) and in the active task (right side).

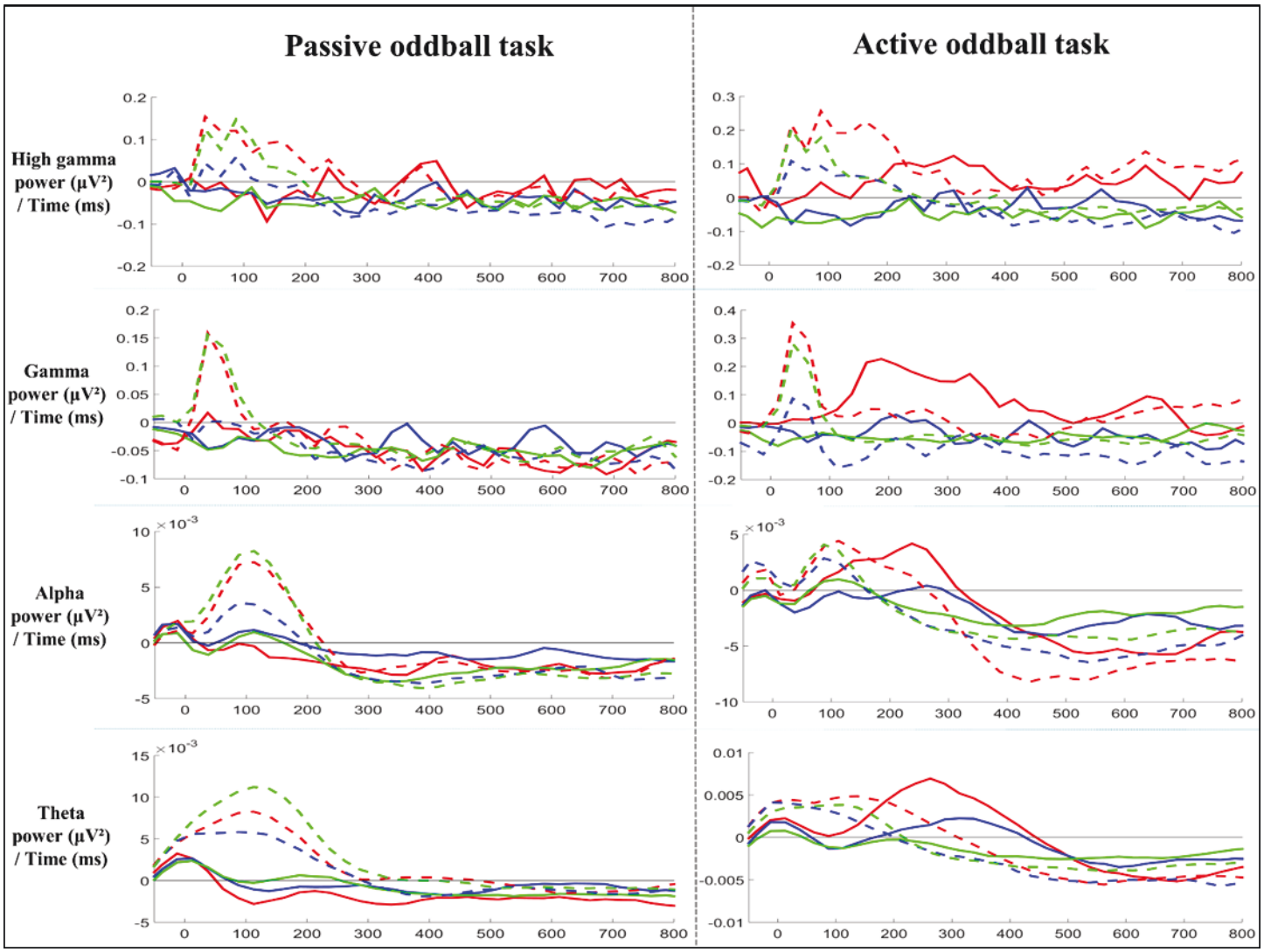


Tableau 4. – ANOVA results for the passive auditory oddball task

		Conditions (Target, Standard, Novel)			**Region (aI, pI)**			**Conditions x Region**		
Frequency	***Interval (ms)***	*F*	*p-value*	*effect*	*F*	*p-value*	*effect*	*F*	*p-value*	*multiple comparisons*
Theta	[50-150]	19.06	< 0.0001	S > T,N	329.91	< 0.0001	aI < pI	7.17	< 0.001	aI T,S,N < pI T,S,N
Alpha	[50-150]	12.86	< 0.0001	S > T,N	200.13	< 0.0001	aI < pI	7.22	< 0.001	aI T,S,N < pI T,S,N
Gamma	[30-100]	11.58	< 0.0001	T > S > N	56.84	< 0.0001	aI < pI	7.17	< 0.001	aI S,N < aI T; pI N < pI S,T
High gamma	[50-150]	5.03	< 0.01	T > S > N	187.56	< 0.0001	aI < pI	5.03	< 0.01	aI T,S,N < pI T,S,N

Abbreviations. T = Target; S = Standard; N = Novel; aI = anterior insula; pI = posterior insula.

Active oddball task

ERP analyses

We observed a significant N100 deflection in 22/28 (79%) (Pt #7 excluded) of pI contacts following target (22/28, 79%), novel (11/28, 39%), and standard (19/28, 68%) stimuli presentation compared to baseline. Amplitudes were significantly greater for target than for novel stimuli (14/22, 64%), for target than for standard stimuli (11/22, 50%), for novel than for standard stimuli (1/11, 9%), and for standard than for novel stimuli (6/19, 32%). These responses were recorded in both the left (13/18, 72%) and the right (9/10, 90%) hemispheres. By contrast, a N100 response was recorded in only 6/32 (19%, all in Pt. #4) of aI contacts for novel (4/32, 13%), standard (6/32, 19%), and target (4/32, 13%) stimuli compared to baseline, and N100 amplitude did not differ between conditions.

P300 responses recorded during the active oddball task are reported in Table 5. Target stimuli elicited a P300 response at 13/32 (41%) of aI contacts (i.e., 5/6 patients with aI contacts). Amplitude was significantly greater for target than for standard stimuli for all of these contacts, and was significantly greater for target than for novel stimuli for 10/13 contacts (77%). Significant responses to target stimuli were observed at the left (10/22, 45%) and at right (3/10, 30%) aI electrode contacts. Mean P300 peak latency in the aI contacts was 329 ms post-target stimulus. In the pI, 11/28 contacts (39.3%) (i.e., 2/4 patients with pI contacts, Pt #7 excluded) showed a P300 response following target stimulus. Amplitude was significantly larger for target than for standard stimuli for all of these contacts, and was significantly larger than for novel stimuli for 8/11 (73%) contacts. Significant responses to target stimuli were observed at the left (6/18, 33%) and right (5/10, 50%) pI electrode contacts. Weighted-average P300 peak latency in the pI was 286 ms post-target stimulus. Very few contacts showed increased P300 amplitude in response to novel vs. standard stimuli (3 in the right aI and 2 in the right pI).

Examples of N100 deflection recorded in the pI contacts and P300 deflection recorded in the aI contacts in response to target stimuli are presented in Figure 3.

Figure 3. – Examples of ERPs recorded at selected insular electrode contacts during the active oddball task. ERPs on the left (A = Pt. 6, B = Pt. 2, C = Pt. 3) show a large negative component peaking around or shortly before 100 ms (N100) in all task conditions; those on the right side (D = Pt. 1, E = Pt. 3, F = Pt. 5) show a large positive component peaking around 250-300 ms (P300) in the target condition only. All significant contacts for a given participant were averaged prior to performing the grand average analysis, so that each participant has the same weight in the resulting ERP (red: target, blue: novel and dark: standard).

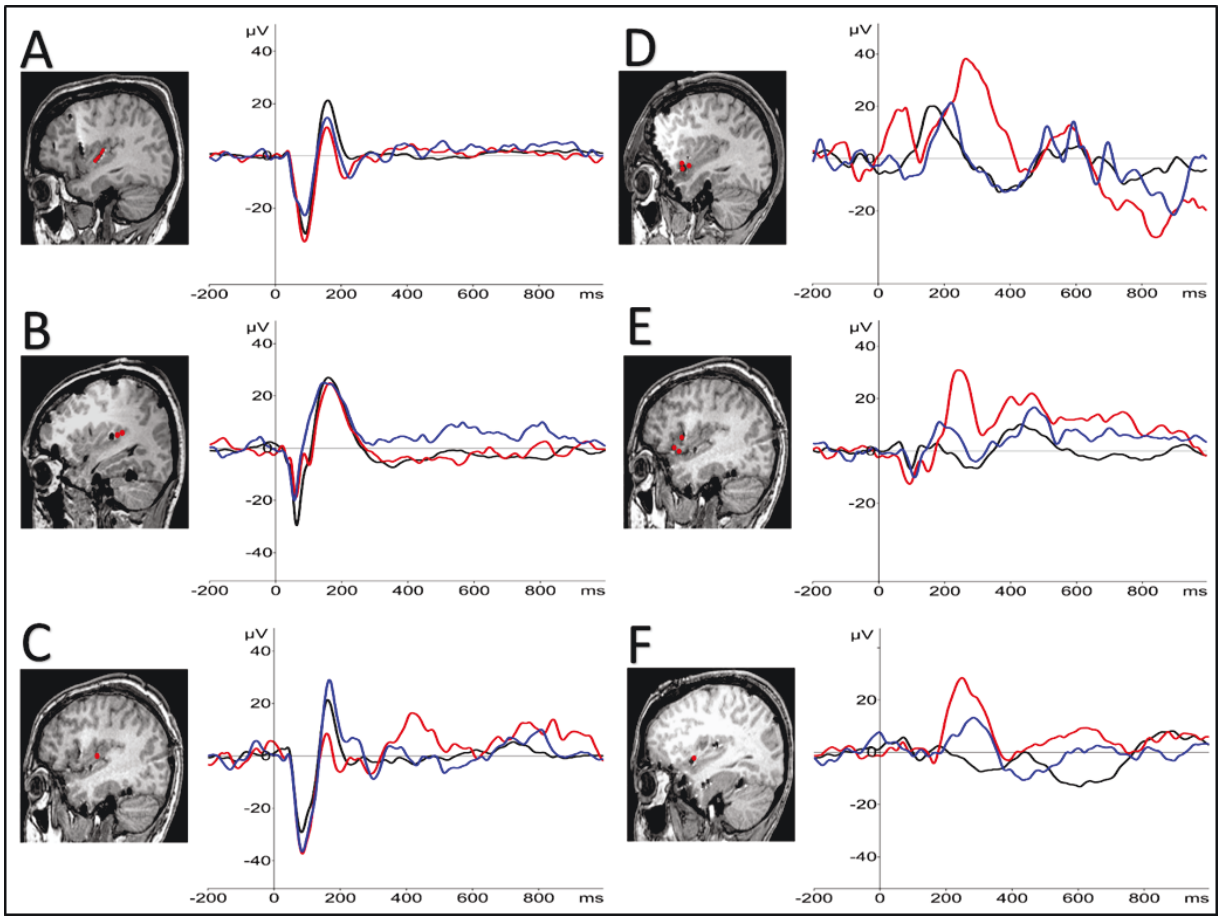


Tableau 5. – P300 (225-400 ms) responses to target stimuli during the active auditory oddball task

Pt. #	Anterior insula						Posterior insula					
	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison
1	u11	Left	as-aps	292 ms	59.74 µV	T>S; T>N						
	u12	Left	as	-	-	-						
	u13	Left	as	-	-	-						
	u31	Left	as	300 ms	20.72 µV	T>S; T>N						
	u32	Left	as	294 ms	34.57 µV	T>S; T>N						
	u52	Left	as	-	-	-						
2							u32	Left	al	-	-	-
							u33	Left	al	-	-	-
							u34	Left	al	-	-	-
3	u11	Left	as-ia	258 ms	39.60 µV	T>S; T>N	u31	Left	pcs	244 ms	22.43 µV	T>S; T>N
	u12	Left	as	230 ms	41.87 µV	T>S; T>N	u32	Left	pcs	266 ms	35.64 µV	T>S; T>N
	u21	Right	as-ms	270 ms	18.57 µV	T>S; T>N	u33	Left	al	-	-	-
							u34	Left	al	-	-	-
							u41	Right	al	368 ms	22.69 µV	T>S; T>N
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
4	u11	Right	ms	342 ms	1.08 µV	T>S; T>N						
	u12	Right	ms	278 ms	0.68 µV	T>S; T>N						
	u13	Right	ms	248 ms	9.14 µV	T>S; T>N						
	u14	Right	ms	-	-	-						
	u15	Right	ms	-	-	-						
	u21	Right	ms	-	-	-						
	u22	Right	ms	-	-	-						
	u23	Right	ms	-	-	-						
5	u13	Left	as	-	-	-	u31	Left	al	-	-	-
	u14	Left	as	-	-	-	u32	Left	al	-	-	-
	u16	Left	as	-	-	-	u33	Left	al	-	-	-
	u17	Left	as	-	-	-	u34	Left	pl	-	-	-
	u35	Left	ms	248 ms	23.60 µV	T>S; T>N						
	u36	Left	as	-	-	-						
6	u11	Left	sis	268 ms	24 µV	T>S						

	u12	Left	ms-sis	-	-	-	u31	Left	cs	-	-	-
	u13	Left	ms-sis	-	-	-	u32	Left	cs-li	-	-	-
	u21	Right	as-ia	-	-	-	u33	Left	al	-	-	-
	u22	Right	ms-sis	398 ms	18.82 μV	T>S	u34	Left	al	286 ms	14.54 μV	T>S; T>N
	u23	Right	ms-sis	394 ms	20.73 μV	T>S	u35	Left	al	284 ms	12.79 μV	T>S; T>N
							u36	Left	al	288 ms	10.01 μV	T>S; T>N
							u37	Left	al	292 ms	10.13 μV	T>S; T>N
							u41	Right	al	296 ms	13.42 μV	T>S; T>N
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	272 ms	6.77 μV	T>S
							u45	Right	al	272 ms	13.42 μV	T>S
							u46	Right	al	270 ms	15.66 μV	T>S
8	u22	Right	as	-	-	-						
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						

Abbreviations. T = Target; S = Standard; N = Novel; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the P300 interval in comparison to baseline are identified with a '-'sign.

Conditions were only compared when waveforms showed significant post-stimulus activity in comparison to baseline.

All significant contacts showed a p-value < 0.01

Time-frequency analyses: mixed-ANOVA models

Results of the mixed-ANOVAs analyses on the active task are shown in Table 6 and illustrated in Figure 2 (right side). As was done for the passive oddball task, the laterality factor was excluded of these analyses as there were no main effect of this factor. In the 50-150 ms time interval, the analyses revealed significant main effects of condition (except in theta frequency band) and region factors, and a significant interaction between these factors, at all frequency bands. Increases in alpha, low- and high-gamma frequency powers were significantly greater for target stimuli than for standard and novel stimuli. Increases in theta, alpha, low- and high-gamma frequency powers were significantly greater at pI than at aI electrode contacts, and were mostly independent of conditions.

In the 250-600 ms time interval, analyses revealed significant main effects of the condition and region factors, and a significant interaction between these factors, at all frequency bands. Increases in theta, alpha, low- and high-gamma frequency powers were significantly greater for target stimuli than for standard and novel stimuli, and were significantly greater at aI electrode contacts compared to pI contacts. Target-specific modulations of high-gamma, low-gamma, alpha, and theta frequency bands were observed at aI electrode contacts (see Table 6, multiple comparisons).

Tableau 6. – ANOVA results for the active auditory oddball task

		Conditions (Target, Standard, Novel)			**Region (aI, pI)**			**Conditions x Region**		
Frequency	***Interval (ms)***	*F*	*p-value*	*effect*	*F*	*p-value*	*effect*	*F*	*p-value*	*multiple comparison*
Theta	[50-150]	2.61	0.07	-	106.3	< 0.0001	aI < pI	0.29	0.75	aI T,S,N < pI T,S,N
	[250-600]	12.47	< 0.0001	T > N > S	50	< 0.0001	aI > pI	9.79	< 0.0001	aI T > aI N > aI S > pI S,T,N
Alpha	[50-150]	9.29	< 0.0001	T > N,S	65.37	< 0.0001	aI < pI	0.92	0.4	aI S,N < pI N,T,S *&* aI T < pI T
	[200-500]	20.12	< 0.0001	T > N,S	10.79	< 0.001	aI > pI	1.16	0.31	aI T > aI S,N; pI S,N
Gamma	[30-100]	21.15	< 0.0001	T > N,S	71.5	< 0.0001	aI < pI	6.87	< 0.001	aI T,N,S; pI N < pI T,S
	[250-600]	67.25	< 0.0001	T > N,S	94.59	< 0.0001	aI > pI	14.97	< 0.0001	aI T > aI S,N; pI S,N,T
High gamma	[50-150]	17.21	< 0.0001	T > N,S	129.23	< 0.0001	aI < pI	1.93	0.14	aI T,N,S; pI S,N < pI T
	[250-500]	36.69	< 0.0001	T > N,S	37.41	< 0.0001	aI > pI	2.15	0.12	aI T > aI S,N; pI S,N,T

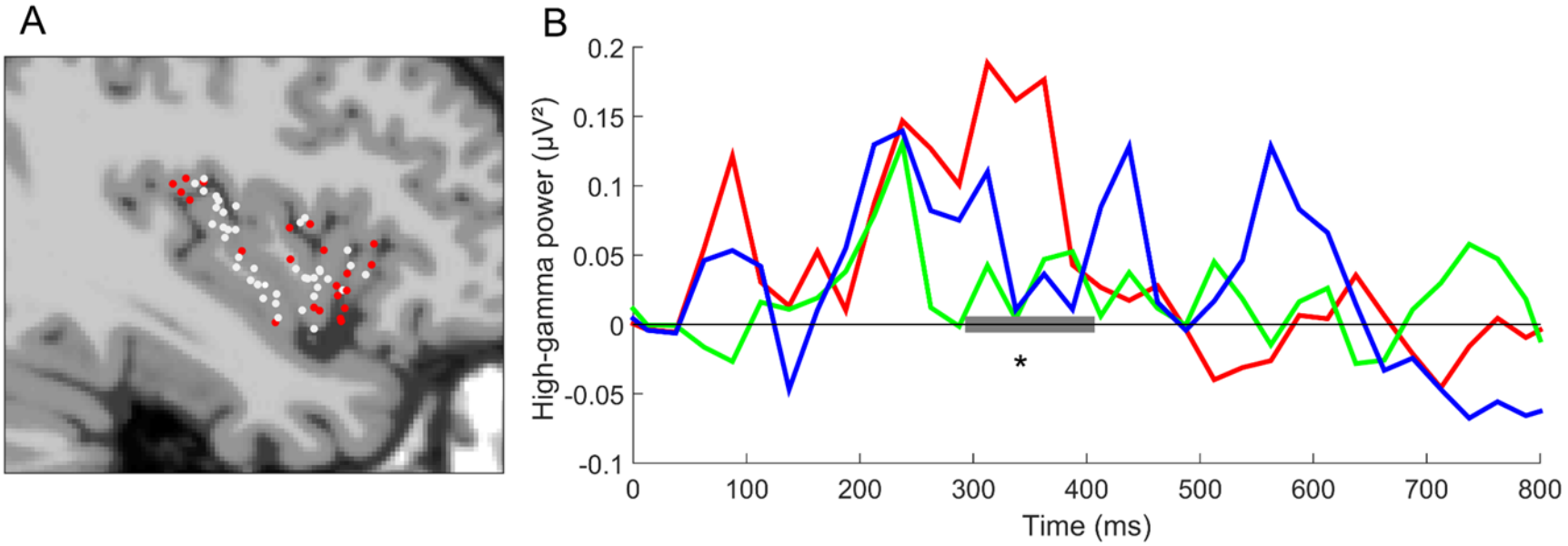
Abbreviations. T = Target; S = Standard; N = Novel; aI = anterior insula; pI = posterior insula

Time-frequency analyses: individual electrode contacts

High-gamma activity. In the 50-150 ms time interval, a significant high-gamma modulation was observed in 5/28 (18%) of pI electrode contacts for target stimuli compared to baseline, and target-dependent high-gamma response was significantly increased for all of these contacts (5/5, 100%) compared to standard and novel stimuli. No aI electrode contacts showed high-gamma activity in this time interval.

In the 200-600 ms interval, 15/32 (47%) aI contacts showed significant high-gamma responses to target stimuli (i.e., 6/6 patients with aI contacts) in comparison to baseline (see Table 7). More specifically, an early (≈ 285 ms) target-specific modulation of high-gamma frequency was observed for 14/15 (93%) of these aI contacts in comparison to standard stimulus, and for 9/15 (60%) in comparison to novel stimulus. Significant responses to target stimulus presentation were observed at the right (4/10, 40%) and left (11/22, 50%) aI electrode contacts. One aI contact showed a late (600 ms) target-dependent modulation. Figure 4 depicts the distribution of insular contacts showing significant target-dependant high-gamma band modulations (A), and mean high-gamma activity of aI significant contacts, relative to baseline (B). By contrast, modulation of high-gamma frequency was observed in the pI in response to target stimuli for 7/30 (23%) contacts. Among these contacts, 4/7 (57%) showed an increased high-gamma response for target compared to novel stimuli. Significant responses to target stimuli presentation were observed at the right (1/12, 8%) and left (6/18, 33%) pI electrode contacts. Only 4/32 (13%) of aI, and 4/30 (13%) of pI of electrode contacts showed a novel-dependent modulation of high-gamma responses in comparison to baseline. For all of these contacts, high-gamma response was increased for novel stimulus compared to standard stimulus.

Figure 4. – (A) Distribution of insular contacts showing significant high-gamma activity in response to target stimuli (red), and no significant high-gamma activity (white) (both hemispheres combined). (B) Average high-gamma activity of aI significant contacts, relative to baseline across conditions (red: target, blue: novel and green: standard).



Low gamma activity. In 50-150 ms time interval, only 4/28 (14%) of pI electrode contacts showed low-gamma responses for target stimuli compared to baseline, and low-gamma activity was increased for all of these contacts (4/4, 100%) for target stimuli compared to novel and standard stimuli. No aI electrode contacts showed low-gamma activity in this time interval.

Table 7 reports low-gamma activity for the time interval of 200-600 ms post-stimuli. A total of 18/32 (56%) of aI electrode contacts showed low-gamma responses to target stimuli (vs. baseline). Target-specific low-gamma modulation was observed for all of these contacts in comparison to standard stimuli (18/18, 100%), and for 13/18 (72%) in comparison to novel stimuli. Significant responses to target stimuli were observed in both the right (4/10, 40%) and left (14/22, 64%) hemispheres for aI electrode contacts. Only 3/28 (11%) of pI electrode contacts showed a target-specific low-gamma modulation (vs. baseline), and for these three contacts low-gamma activity was more strongly increased for target stimuli compared to standard stimulus.

Alpha activity. Very few contacts showed a target-specific alpha modulation in the 50-150 ms time interval compared to the baseline (2/28, 7% in pI, and 2/32, 6% in aI). Alpha activity was significantly increased for targets compared to standard stimulus.

Alpha-band modulations in the time interval of 200-600 ms post-stimuli are reported in Table 7. An early and long-lasting (≈ 200-500 ms) response to target stimuli (vs. baseline) was observed in the alpha frequency band for 21/32 (67%) of aI electrode contacts. Among these contacts, a target-specific modulation was observed for 21/21 (100%) in comparison to standard stimulus, and for 8/21 (38%) in comparison to novel stimulus. Significant responses to target stimuli were observed at the right (7/10, 70%) and left (14/22, 64%) hemispheres for aI electrode contacts. Only 2/28 (7%) of pI electrode contacts showed a target-dependent alpha modulation (vs. baseline), and for these two contacts, alpha activity was more strongly increased for target compared to standard stimulus.

Theta activity. In the 50-150 time interval, analyses revealed a significant modulation of theta activity for pI electrode contacts (10/28, 36%, all conditions confounded) compared to baseline, and theta modulations were significantly increased for standard stimuli compared to targets (4/10, 40%), and compared to novel stimulus (1/10, 10%), but the opposite pattern was also found (target > standard: 3/10, 30%; novel < standard: 2/10, 20%), and for target stimuli compared to novel (3/10, 30%). By contrast, only 5/32 (16%) of aI electrode contacts showed theta responses for target stimuli relative to baseline, and for all of these contacts (5/5, 100%), theta activity was significantly increased for target stimuli compared to standard and novel stimuli.

Results regarding theta modulation in the time interval of 200-600 ms post-stimuli are reported in Table 7. An early and long-lasting (≈ 200-500 ms) response to target stimuli (vs. baseline) was observed in the theta band for 29/32 (91%) of aI contacts. Among these contacts, target-specific modulation of theta frequency was observed for 29/29 (100%) in comparison to standard stimulus, and for 5/29 (17%) in comparison to novel stimulus. Significant responses to target stimuli were observed at the right (9/10, 90%) and left (20/22, 91%) for aI electrode contacts. By contrast, only 4/28 (14%) of pI electrode contacts showed a target-dependent theta modulation relative to the baseline. For all of these contacts, theta activity was significantly increased for target stimulus compared to standard stimulus, and compared to novel for two contacts. The distribution of insular contacts showing theta band modulations for target stimulus compared to standard stimulus (A) and mean theta activity of aI significant contacts relative to baseline (B) are illustrated in Figure 5.

Tableau 7. – Modulations of oscillatory activity in response target stimuli during the active auditory oddball task

				Anterior insula							
				High-gamma (70-150 Hz)		Low-gamma (30-50 Hz)		Alpha (8-12 Hz)		Theta (4-7 Hz)	
Pt.	Contact	Side	Gyrus	Difference	Time (ms)	Difference	Time (ms)	Difference	Time (ms)	Difference	Time (ms)
1	u11	Left	as-aps	T>S	300	T>S; T>N	300-400	-	-	T>S; T>N	300-500
	u12	Left	as	-	-	T>S; T>N	500	-	-	T>S	250-400
	u13	Left	as	T>S; T>N	600	-	-	T>S	200-300	T>S; T>N	350-500
	u31	Left	as	T>S	200	T>S	300	-	-	T>S	300-400
	u32	Left	as	T>S	300	-	-	-	-	T>S; T>N	350-400
	u52	Left	as	-	-	-	-	-	-	T>S; T>N	250-400
3	u11	Left	as-ia	T>S; T>N	400	-	-	-	-	T>S	200-300
	u12	Left	as	-	-	T>S; T>N	200-300	T>S; T>N	200-250	T>S	200-300
	u21	Right	as-ms	-	-	-	-	-	-	-	-
4	u11	Left	ms	-	-	-	-	T>S	250-300	T>S	200-400
	u12	Left	ms	-	-	T>S	500	T>S	250-400	T>S	200-400
	u13	Left	ms	-	-	-	-	T>S; T>N	250-500	T>S; T>N	200-400
	u14	Left	ms	-	-	-	-	T>S; T>N	200-400	T>S; T>N	200-400
	u15	Left	ms	-	-	-	-	T>S	250-400	T>S; T>N	200-400
	u21	Right	ms	T>S	200	-	-	T>S	250-500	T>S	200-400
	u22	Right	ms	-	-	-	-	T>S; T>N	300	T>S	200-400
	u23	Right	ms	-	-	-	-	-	-	T>S	200-400
5	u13	Left	as	T>S	400-500	T>S	200-350	T>S	250	T>S	250-300
	u14	Left	as	-	-	T>S	200-350	-	-	T>S	250-350
	u16	Left	as	-	-	T>S	250	T>S	350-500	-	-
	u17	Left	as	T>S; T>N	400-500	T>S; T>N	250	T>S	300-500	-	-
	u35	Left	Ms	T>S; T>N	200-500	T>S; T>N	250-500	T>S	350-500	T>S	250-500
	u36	Left	as	T>S; T>N	200-500	T>S; T>N	300-500	T>S	300-400	T>S	250-500
6	u11	Left	sis	-	-	T>S; T>N	200-450	T>S	450-500	T>S	250-300
	u12	Left	ms-sis	T>S	300	T>S; T>N	250-600	T>S; T>N	400-450	T>S	250-300
	u13	Left	ms-sis	T>S; T>N	400-500	T>S; T>N	250-600	-	-	T>S	200-400
	u21	Right	as-ia	-	-	-	-	-	-	T>S	250-400
	u22	Right	ms-sis	-	-	-	-	T>S	500	T>S	250-400
	u23	Right	ms-sis	-	-	T>S; T>N	250-600	T>S	450-500	T>S	250-400
8	u22	Right	as	T>S; T>N	300-400	T>S; T>N	200-600	T>S; T>N	200-400	T>S	250-400
	u23	Right	as	T>S; T>N	200-300	T>S; T>N	200-500	T>S	300-400	T>S	300-500
	u24	Right	as	T>S; T>N	200-300	T>S; T>N	200-600	T>S; T>N	450-500	T>S	250-450

				Posterior insula							
				High-gamma (70-150 Hz)		Gamma (30-50 Hz)		Alpha (8-12 Hz)		Theta (4-7 Hz)	
Pt.	Contact	Side	Gyrus	Difference	Time (ms)	Difference	Time (ms)	Difference	Time (ms)	Difference	Time (ms)
2	u32	Left	al	T>S	200-600	-	-	-	-	-	-
	u33	Left	al	T>S	200	-	-	-	-	-	-
	u34	Left	al	T>S	300-500	-	-	-	-	-	-
3	u31	Left	pcs	-	-	T>S	300	-	-	-	-
	u32	Left	pcs	-	-	-	-	-	-	-	-
	u33	Left	al	-	-	T>S; T>N	450	-	-	-	-
	u34	Left	al	-	-	T>S; T>N	400-600	-	-	-	-
	u41	Right	al	-	-	-	-	T>S	200-400	-	-
	u42	Right	al	-	-	-	-	-	-	-	-
	u43	Right	al	-	-	-	-	-	-	-	-
	u44	Right	al	-	-	-	-	-	-	-	-
5	u31	Left	al	T>S; T>N	200-600	-	-	-	-	T>S; T>N	250-400 ms
	u32	Left	al	T>S; T>N	200-600	-	-	-	-	T>S; T>N	250-450 ms
	u33	Left	al	-	-	-	-	-	-	-	-
	u34	Left	pl	-	-	-	-	-	-	-	-
6	u31	Left	cs	T>S; T>N	400	-	-	-	-	T>S	300 ms
	u32	Left	cs-li	-	-	-	-	-	-	-	-
	u33	Left	al	-	-	-	-	-	-	-	-
	u34	Left	al	-	-	-	-	-	-	-	-
	u35	Left	al	-	-	-	-	-	-	-	-
	u36	Left	al	-	-	-	-	-	-	-	-
	u37	Left	al	-	-	-	-	T>S	350 ms	-	-
	u41	Right	al	-	-	-	-	-	-	-	-
	u42	Right	al	T>S; T>N	400 ms	-	-	-	-	-	-
	u43	Right	al	-	-	-	-	-	-	T>S	300-400 ms
	u44	Right	al	-	-	-	-	-	-	-	-
	u45	Right	al	-	-	-	-	-	-	-	-
	u46	Right	al	-	-	-	-	-	-	-	-

Abbreviations. T = Target; S = Standard; N = Novel; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the time interval analyzed (200 – 600 ms for low-gamma and high-gamma; 200 – 500 ms for theta and alpha) in comparison to baseline are identified with a '-'sign. Conditions were only compared when waveforms showed significant post-stimulus activity in comparison to baseline.

Figure 5. – (A) Distribution of insular contacts showing significant theta activity in response to target stimuli (red), and no significant theta activity (white). (B) Average theta activity of aI significant contacts, relative to baseline across conditions (red: target, blue: novel and green: standard).

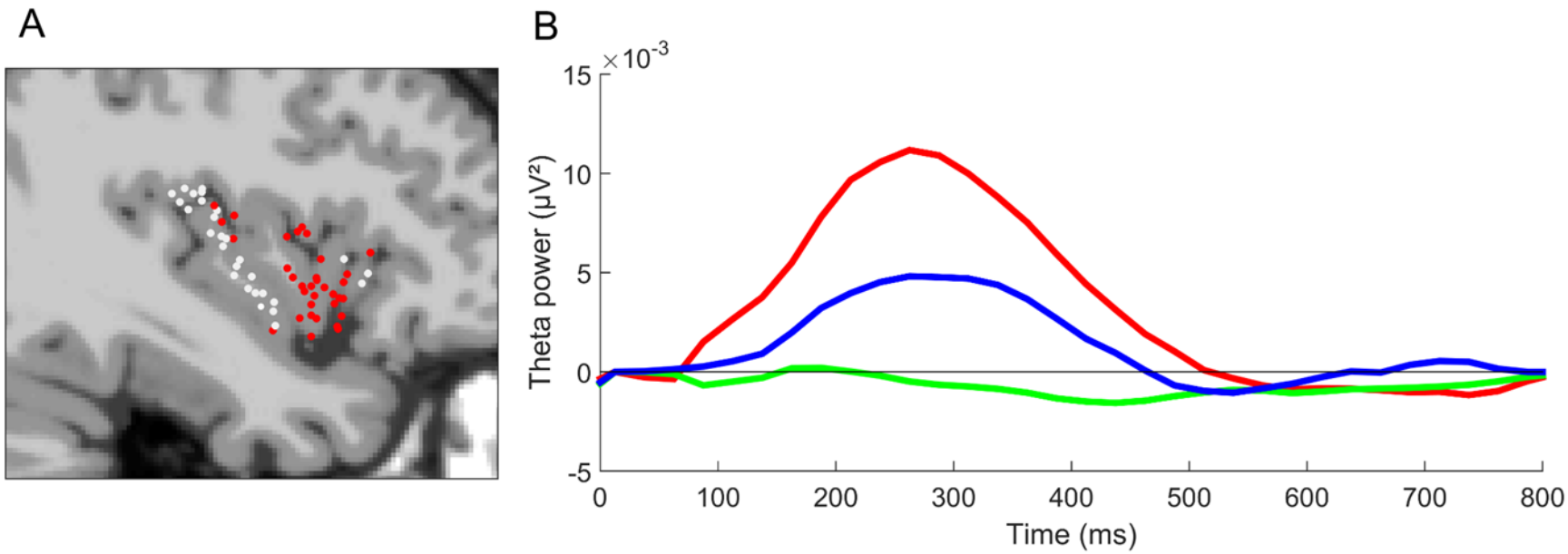


Tableau 8. – Supplemental Table S1. Total of trials retained in each task condition per insula, expressed in percentages. All electrode contacts per insula were averaged for each participant.

		Frequency task				**Active oddball task**			**Passive oddball task**		
		500 Hz	1,000 Hz	2,000 Hz	4,000 Hz	Target	Novel	Standard	Target	Novel	Standard
P1 # 1	*ERP*	40 (3.3)	40 (2)	36 (1.9)	39 (2.5)	38 (13)	37 (11.3)	40 (11.8)	84 (2.4)	76 (2)	84 (1.2)
	Time-frequency	26 (1.9)	26 (1.7)	22 (0.9)	23 (0.7)	31 (12.5)	29 (11.6)	34 (12.7)	80 (3.1)	73 (2)	75 (1.6)
Pt # 2	*ERP*	54 (0.4)	59 (0)	51 (0)	56 (0.4)	60 (1.1)	71 (0.6)	74 (0.1)	82 (0.6)	74 (1.1)	77 (0.4)
	Time-frequency	42 (0.4)	36 (0.4)	39 (0)	37 (0)	59 (1.1)	64 (0)	66 (0.3)	75 (0.6)	70 (1.1)	69 (0.3)
Pt # 3	*ERP*	60 (2.7)	64 (2.5)	58 (2.4)	52 (2.7)	67 (3.7)	67 (4.6)	70 (4.6)	73 (3.8)	75 (4.4)	74 (4.6)
	Time-frequency	43 (2.7)	46 (2.3)	44 (2.4)	40 (2.3)	59 (5.5)	59 (5.5)	61 (5.7)	60 (4.8)	63 (8.1)	64 (4.9)
Pt # 4	*ERP*	62 (8.3)	62 (10.1)	64 (7.9)	63 (7.4)	46 (5.7)	53 (3.6)	51 (3.8)	69 (7.3)	80 (6.6)	80 (6.6)
	Time-frequency	48 (8.8)	48 (10.3)	52 (7.9)	53 (7.6)	42 (6.2)	48 (5.7)	43 (4)	64 (7.2)	70 (8.3)	77 (7.6)
Pt # 5	*ERP*	61 (10.5)	61 (12.5)	59 (11.4)	62 (11.9)	89 (8.1)	87 (5.8)	86 (7.3)	82 (8.7)	85 (10.4)	85 (6.2)
	Time-frequency	47 (10.7)	47 (11.4)	45 (10.3)	44 (10.6)	88 (9.3)	83 (8.3)	81 (8.9)	81 (9.9)	81 (10.1)	81 (7.6)
Pt # 6	*ERP*	29 (7.8)	29 (7.6)	28 (6.9)	30 (7.4)	65 (6.1)	79 (4.9)	76 (4.6)	54 (14.7)	50 (16.1)	55 (15.6)
	Time-frequency	15 (5)	20 (6.5)	17 (6.2)	19 (6.5)	60 (6.5)	69 (6.8)	70 (5.8)	40 (18.1)	42 (18)	43 (17.7)
Pt # 7	*EPR*	50 (0.5)	46 (0.5)	42 (1.4)	45 (0.5)	-	-	-	57 (1.6)	53 (3.1)	56 (2.2)
	Time-frequency	33 (0.5)	31 (1.4)	27 (0.5)	30 (0.5)	-	-	-	49 (2.4)	48 (0.8)	47 (1.7)
Pt # 8	*ERP*	-	-	-	-	70 (8.9)	80 (5.6)	82 (4.8)	90 (4.2)	78 (4)	82 (6)
	Time-frequency	-	-	-	-	64 (8.9)	74 (8.4)	75 (6.9)	84 (1.3)	71 (6.1)	75 (7.4)

Discussion

We studied the contribution of the human insula to auditory information processing by examining ERPs and modulations of theta, alpha, low- and high-gamma iEEG activity recorded during two passive listening tasks and one three-stimulus auditory oddball detection task, in eight epileptic patients during their pre-surgical evaluation for drug-resistant epilepsy. A vast majority of contacts in the pI (i.e., 79% and 83%) showed an N100 response around 100 ms following auditory stimuli, independently of task and condition. Furthermore, in the passive auditory oddball task, theta and alpha band responses were greater at pI electrode contacts compared to aI contacts in the 50-150 ms time interval, independently of task conditions. These results suggest that the pI is involved in automatic sensory information processes. By contrast, a significant proportion (41%) of aI contacts showed a P300 wave following target detection around 300 ms post-stimulus in the active auditory oddball task. Time-frequency analyses conducted in the 250-600 ms time interval of the active oddball task showed target-specific modulations in the theta, alpha, low- and high-gamma frequency bands preferentially at aI contacts. More specifically, a high proportion of aI contacts showed theta (91%), alpha (67%), low-gamma (56%), and high-gamma (47%) modulations to target stimuli. These results highlight the involvement of the aI in voluntary and controlled auditory attentional processing.

Several neuroimaging and clinical studies suggest a critical role of the insula in auditory processing (Bamiou et al. 2003; Griffiths et al. 2004; Boucher et al. 2015b), and electro-cortical stimulation studies further support involvement of the pI in sensory information processing (Isnard et al. 2004; Nguyen et al. 2009; Afif et al. 2010). In our study, most of the pI contacts showed an N100 response, which was not significantly modulated by task conditions. This result suggests that the pI participates in early, involuntary processing of auditory information occurring about 100 ms post-stimuli. Surprisingly, we also observed N100 responses in the middle short insular gyrus in one patient

(Pt. #4), in both oddball tasks. More specifically, the electrode contacts located more dorsally in the middle short gyrus of this patient responded early to auditory stimuli, whereas those located ventrally specifically responded to target stimuli. Although few studies support an involvement of the anterior and the intermediate insular regions in early auditory processing, two stimulation studies have shown auditory disturbances following direct electrical stimulation in the aI (Isnard et al. 2004; Afif et al. 2010).

In accordance with previous neuroimaging studies (Stevens et al. 2000; Ackermann et al. 2001; Nelson et al. 2010; Chen et al. 2015), we found that the aI responds preferentially to target stimuli, highlighting its role in selective attentional processing. Our findings suggest that auditory target detection is associated with a P3b response in the aI occurring around 300 ms post-stimuli, which underlies top-down attentional processing. We recently reported similar findings using visual stimuli, suggesting that this response is independent of the sensory modality (Citherlet et al. 2019). Contrary to our expectations, several pI contacts have also shown a P3b response following target stimuli in two out of four patients with pI contacts. Clark et al. (2000) also reported bilateral precentral (i.e., aI) and post-central (i.e., pI) insula activations following target detection in an event-related fMRI study. We found no difference in P300 amplitude or latency between aI and pI contacts for these two patients. One plausible explanation could be related to complex functional connectivity between insular subregions, which can explain the integration of auditory information processing across aI and pI (Almashaikhi et al. 2014).

Although event-related fMRI studies have reported aI activation for novel auditory stimuli (Downar et al. 2000; Kiehl et al. 2001), we did not observe P3a responses in the aI for novel-irrelevant stimuli. Our results are congruent with what we found with visual stimuli (Citherlet et al. 2019) and suggest that the aI does not respond preferentially to rare stimuli, but rather to task-relevant stimuli,

as previously suggested by Nelson (Nelson et al. 2010). However, due to the crucial role of the aI in affective processing, we cannot exclude the possibility that the aI is involved in bottom-up attentional processing of irrelevant stimuli, for affectively relevant-novel stimuli (Phan et al. 2004; Britton et al. 2006; Berntson et al. 2011; Uddin et al. 2017; Koelsch et al. 2018).

In the passive oddball task, we observed a stronger increase of theta, alpha, low- and high-gamma responses in pI contacts than in the aI region at 50-150 ms post-stimulus, independent of task conditions. Analyses of individual pI electrode contacts showed that theta (30%) and alpha (27%) modulations were more observable than low- and high-gamma (< 10%) frequency in this time interval. These results suggest that the pI is involved in automatic sensory processes, as supported by early theta and alpha frequency modulations for auditory stimuli (Hsiao et al. 2009; Karrasch et al. 1998; Ko et al. 2012; Krause et al. 1994, 1996). Contrary to a study by Edwards and colleagues (2005) which suggested that gamma activity can be generated without voluntary attention, we found few gamma modulations (< 10% of pI contacts) in the passive oddball task. In the active task, frequency modulations at pI contacts were similar to those observed in the passive task in the 50-150 ms post-stimulus time interval, also supporting a role of this insular portion in an early attentional processing. Interestingly, no aI contacts showed low- or high-gamma responses, which indicates clear dissociation between pI and aI regions in sensory attentional processing.

In the aI region, target detection was associated with an increase of theta, alpha, and high- and low-gamma modulations compared to standard and novel stimuli around 200-600 ms post-stimulus, reflecting voluntary attentional processing. Despite the fact that some previous studies have reported that an increase in gamma activity is accompanied by a decrease in low frequency bands (Fries et al. 2001; Jensen and Mazaheri, 2010), we observed both low- and high-frequency bands involved in voluntary attentional processing, as proposed by other studies showing the presence of

low-frequency oscillatory in selective attentional processing (Öniz and Basar, 2009; Sauseng et al. 2006; Schroeder and Lakatos 2009; Womelsdorf and Fries 2007). Canolty et al. (2006) have also reported that high-gamma frequency was phase locked to theta oscillations.

More specifically, we observed early theta (91%) and alpha (67%) responses in relation to target detection around 200-500 ms post-stimulus for a large proportion of aI contacts, reflecting an active discrimination processing as suggested by Ko and colleagues for the theta frequency band (Ko et al. 2012). Thus, theta and alpha responses to targets in the aI highlight the contribution of this area in top-down attentional processing. However, several studies reported that alpha oscillations reflect a state of functional inhibition, and therefore alpha activity typically decreases in regions involved in the task and increases in task-irrelevant regions (Bonnefond and Jensen 2015; Foxe and Snyder 2011; Jensen and Mazaheri 2010; Jokisch and Jensen 2007; Klimesch et al. 2012). By contrast, we found target-specific alpha oscillations in the aI region, supporting the occurrence of alpha oscillations in task-relevant regions (see Klimesch et al. 2000). This apparent contradiction can be explained by the different types of time-frequency analyses conducted, namely phase-locked oscillations (i.e., evoked-related activity), which contribute to the generation of ERP components like the N100 and P300 waves (Crone et al. 2001; Hsiao et al. 2009; Klimesch et al. 2004; Demiralp et al. 2001; Karakas et al. 2000; Klimesch et al. 2004; Öniz and Basar, 2009), and time-locked oscillations (i.e., induced-related activity). Increases in evoked alpha responses have been found after stimulus onset, whereas decreases of induced alpha are typically reported (Brandt et al. 1997; Herrmann and Knight, 2001; Klimesch et al. 2000). As our time-frequency results are based on evoked-related oscillations, we observed alpha activity increases in the P300 ERP time interval.

Our results suggest that target detection is associated with high-gamma (47%) and low-gamma (56%) modulations of aI contacts around 200-600 ms post-stimuli. This suggests that the aI is

involved in active sound discrimination, reflecting a top-down attentional processing (Ray et al. 2008; Cervenka et al. 2011). We found very few significant differences in the gamma range (30-150 Hz) between the novel and standard stimuli, suggesting that the aI is involved in goal-directed processing rather than in stimuli-irrelevant processing, as previously suggested by Debener (Debener et al. 2003). Low- and high-gamma responses have been suggested to reflect distinct phenomena reflecting different aspects of cognitive function (Crone et al., 2001; Edwards et al., 2005). For example, Ray and colleagues (Ray et al., 2008) have reported that the entire gamma range (30-150 Hz) appears at an early stage related to stimulus-induced responses while voluntary attentional-related modulation involves specifically high-gamma activity (> 60 Hz). In our study, we did not find such distinction within the gamma frequency range in attentional processing. The smaller number of high-gamma responses in aI may be partially due to the fact that high-gamma oscillations are normally involved in more complex acoustic features of speech (Crone et al., 2001, 2007).

P3b responses, as well as alpha, theta, and low- and high-gamma modulations were observed in both the left and the right insulae, in both involuntary and voluntary attentional processes. In contrast with previous studies, which have suggested that the right insula is more involved in salience processing (Downar et al. 2000; Uddin 2015), our results on ERPs and time-frequencies do not support such a hemispheric dominance in voluntary attentional processing. However, it is important to consider that several studies have reported the participation of the right aI following affective-relevant stimuli (Paulus et al. 2003; Terasawa et al. 2015). Again, we cannot exclude such laterality dependency with affective targets stimuli presentation. Furthermore, we did not find a preferential response in the right aI for low-frequency tones as previously suggested by Ackermann (Ackermann et al. 2001). Our results do not support a specific processing for any frequency tones in the insula. Furthermore, regarding our N100 ERP response distribution, we cannot exclude the possibility that

the superior insular region is more involved in early attentional processing for auditory stimuli than the inferior region, which would be congruent with its connections with auditory areas (Ghaziri et al. 2018). Finally, although prior studies have suggested a preferential role of the dorsal aI in cognitive processing and a role of the ventral aI in socio-emotional processing (Kurth et al., 2010), we observed target-specific responses in both the ventral and dorsal subportions of the aI.

Limitations of this study include factors that are inherent to iEEG studies with epileptic patients, i.e. the possible influence of epilepsy and associated pathology on the functional reorganisation of the brain, the influence of medication on neural activity, and the incomplete coverage of the brain by intracranial electrodes that limits the generalisation of our findings. Another limitation to our protocol is that frequencies were not counterbalanced to avoid frequency-related biases in the deviance responses observed. However, the absence of pattern suggesting greater (or smaller) amplitude for any tone frequency in the first (frequency) task suggests that task instructions, and not frequencies, are responsible for the observed differences across conditions. Despite these limitations, our results are generally consistent across participants and are congruent with prior studies.

To our knowledge, this study is the first to examine the spatiotemporal dynamics of auditory information processing in the entire insular cortex using iEEG. Our findings suggest that the pI is involved in automatic auditory processing, indexed by a N100 response and an increase of theta, alpha, low- and high-frequency power following any auditory stimulus. We recorded a P3b response in the aI following auditory target detection, underlying voluntary attentional processing. Theta, alpha, low- and high-gamma modulations were also recorded in response to target stimuli in the aI, confirming its involvement of this area in top-down processing.

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CHAPITRE III : ÉTUDES EN ÉVALUATIONS CLINIQUES

ARTICLE III

SENSORY PROFILE ALTERATIONS IN PATIENTS WITH INSULAR EPILEPSY SURGERY: PRELIMINARY FINDINGS.

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Abstract

The insular cortex is now well-established as a potential site of epileptogenesis in patients with drug-resistant epilepsy, and its resection has been associated with good outcomes in terms of seizure control. However, given the role of the insula in sensory processing and in visceral information integration, it remains unclear whether insular cortex epilepsy and its surgery are associated with disturbances in sensory information processing and visceral sensation processes as experienced in daily life. In the present study, we examined such sensory disturbances in a group of patients (n = 17) who underwent epilepsy surgery involving a resection of the insula, and compared them to a lesion-control group of patients with temporal epilepsy surgery (n = 22) and a healthy control group (n = 29) matched for age, gender, and education. Participants were assessed on the self-report "Adolescent/Adult Sensory Profile" questionnaire at least four months after surgery. Our series of one-way analyses of variance (ANOVAs) revealed that insular and temporal resections in patients with drug-refractory epilepsy were associated with a low "sensation seeking" behavior reflecting a lack of engagement with sensory inputs from the environment. Furthermore, insular resections were associated with impairments in the "active behavioral responses" for the gustatory/olfactory modalities. These preliminary findings suggest that insular resections may be associated with mild to moderate alterations in sensory processing.

Keywords: Insula; Epilepsy; Sensory profile; Sensation seeking; "Adolescent/Adult Sensory Profile" questionnaire; Gustatory/Olfactory Modalities

Introduction

The insular cortex, considered as the fifth and smallest lobe of the brain, is a multimodal structure that integrates sensory inputs arising from outside the body (i.e., auditory, somatosensory, olfactory, gustatory, and visual information) and sensations from inside the body (i.e., visceral information) [1, 2]. This paralimbic structure located deep in the Sylvian fissure is divided into an anterior and a posterior part by the central insular sulcus [3]. Both insular parts are involved in the integration of internal and external environment signals through a caudo-rostral projection of the information [4, 5]. Indeed, interoceptive information on constantly changing body states reaches the posterior part through ascending sensory inputs and are then projected to the anterior part where interoceptive information is integrated with cognitive, emotional, and motivational signals collected by cortical and subcortical regions [4, 6]. Given the extensive connectivity of the insula (e.g., orbitofrontal cortex, superior temporal sulcus, primary auditory cortex, and auditory association cortex, somatosensory areas, olfactory bulb/tubercle, perirhinal, and entorhinal cortex), it is not surprising that the insula is associated with a multitude of functions such as sensory, cognitive, and socio-affective functions [7, 8].

Several studies using direct electro-cortical stimulation in patients undergoing invasive iEEG monitoring of epileptic seizures as part of a pre-surgical evaluation or undergoing neurosurgery have reported that stimulating neurons in the insula generates a variety of physiological responses, including somatosensory (e.g., warmth sensation, tingling, numbness, and pain in the body), visceral (e.g., nausea and abdominal buzz), and vestibular (e.g., vertigo) responses. Sensory responses have also been reported, such as auditory (e.g., echoing sounds, auditory hallucinations, buzzing, and whistling) and olfacto-gustatory (e.g., pleasant odor, unpleasant taste, hallucinations, salivation, and metallic taste) phenomena [9-13]. Furthermore, studies with patients with insular lesions have

documented cases of altered auditory processing, manifested by agnosia to environmental sounds, musical anhedonia, hyperacusis, and disturbances in speech sound identification [14-16]. Although less reported, disturbance in intensity processing of tastes and odors have been also suggested [17-19]. Thus, findings from electro-cortical stimulation and lesion studies suggest that the insula is involved in multisensory processing. Neuroimaging studies as well have reported insular activations in response to auditory, gustatory, and olfactory stimuli, and visceral sensations [20-22], further supporting the role of this structure in processing information incoming of these sensory modalities.

The insula has been found to be involved in the epileptogenesis of a non-negligible proportion of patients with drug-resistant epilepsy [10, 13]. Resection of an insular epileptic focus has been associated with good outcomes in terms of seizure control and of cognitive processes sequelae [23-25]. Besides a few case studies with patients reporting sensory disturbances [23, 26], no study has yet systematically investigated somatosensory processing in patients who have undergone insular resection as part of their epilepsy surgery for drug-resistant seizures. Using the self-administered Adolescent/Adult Sensory Profile (AASP) questionnaire [27], the present study sought to determine whether insular cortex resection is associated with multisensory disturbances, as experienced in day-to-day life. Given the well-established role of the insula in chemosomatosensory processing, we hypothesized that insular resection would be associated with global impairments in sensory information processing compared with the temporal and control groups. More specifically, we expected mild to moderate sensory disturbances in taste/smell, tactile, auditory, and visceral modalities in the insular group and an increased sensitivity associated with the insular resection.

Method and Material

Participants

Our sample included seventeen patients (14 females; mean age = 42 years, SD = 7.6) who underwent insular resection for drug-resistant epilepsy in our epilepsy service during the period extending from 2004 to 2018 and a lesion-control group of 22 patients (15 females; mean age = 43 years, SD = 11.9) who underwent temporal lobe epilepsy surgery including amygdalo-hippocampectomy between 2003 and 2018 to control for epilepsy diagnosis and surgery (see Table 1 for more details concerning the insular patients). All patients were tested at least four months after surgery. Patients were invited by phone to partake in this study, and participants were then sent a series of questionnaires at their home by mail, along with the institutional consent form and a pre-addressed envelope to be sent back to our center. Another group of 29 adults (20 females; mean age = 38 years, SD = 11.9), matched for gender, age and education, were also recruited using ads on our center's intranet website to form the healthy control group. A monetary compensation of 20 Canadian dollars was offered upon completion of the questionnaires. This study was approved by the Research Ethics Committee of the CHUM.

Tableau 1. – Demographic and surgery-related characteristics of the insular resection group

Pt.	Gender	Education (y)	Time since surgery (y)	Age at surgery (y)	Location of surgery				Engel's classification of outcome
					Side	Insular area	Insular resection (%)	Opercular area	Other areas	
I1	f	11	2.6	34	R	AI-MI-MS-PI-PS	65	T op	SAH	III
I2	f	14	2,7	36	R	AI-MI-PI	35	T op	ATL	I
I3	f	12	5.1	36	R	MI-MS-PI-PS	45	P op	RIA	I
I4	f	15	2,6	52	L	AI-AS-MI-MS	75	T op	ATL	I
I5	f	15	5,6	23	R	AI-AS-MI-MS-PI-PS	95	F-T-P op	RIA	III
I6	m	13	0,4	23	R	AI-AS-MI-MS	65	F op	-	III
I7	f	15	5,3	36	R	MI-MS-PI-PS	75	T-P op	RIA	IV
I8	f	13	9,7	40	L	AI-AS-MI-MS	65	T op	ATL	III
I9	m	13	2,5	34	R	AI-MI-PI	35	T op	SAH	I
I10	f	16	6.3	28	R	AI-MI	15	-	OFC	I
I11	f	13	0,5	31	R	AI-AS-MI-MS-PI-PS	95	T op	SAH	I
I12	f	11	4,0	49	R	AS-MS-PS	55	F-P op	-	I
I13	f	12	2,7	35	R	AI-AS-MI-MS	45	F op	OFC	II
I14	f	7	13,6	23	R	AI-MI-MS-PI-PS	75	T op	ATL	I
I15	f	11	3,9	34	L	MS-PS	25	P op	-	I
I16	f	12	5,4	39	L	AI-AS-MI-MS	75	F-T op	-	I
I 17	m	11	4,1	50	R	AI-AS-MI-MS	55	F op	OFC	I

Note: Resected insular subregions. AI = anterior inferior; AS = anterior superior; MI = intermediate inferior; MS = intermediate superior; PI = posterior inferior; PS = posterior superior.
Abbreviations: ATL = anterior temporal lobe; f = female; F = frontal; L = left; m = male; OFC = orbitofrontal cortex; op = operculum; P = parietal; R = right; RIA = retro-insular area; SAH = selective amygdalo-hippocampectomy; T = temporal

Sensory Profile Questionnaire

The French version of Dunn's AASP [27] was used to assess sensory processing. This self-report questionnaire is designed as a trait measure of sensory processing, reflecting the effect of sensory processing on functional performance. The AASP is composed of 60 items describing behaviors to everyday sensory experiences. Items cover the sensory processing categories of taste/smell, movement, visual, touch, activity level, and auditory. The participant is asked to indicate how he or she generally responds to sensations on a 5-level Likert type scale (1 = almost never; 5 = almost always).

Based on Dunn's Model of Sensory Processing [28], four quadrants scores are obtained from the summation of 15 items, with scores ranging from 15 to 75: the "low registration," "sensation seeking," "sensory sensitivity," and "sensation avoiding." These four quadrants are presented in a conceptual model that proposes an interaction between two continua components: the behavioral responses (i.e., self-regulation strategies, from passive to active) and individual's neurological thresholds (i.e., responsiveness, from low to high). The *low registration* refers to a low awareness of sensations, requiring high intensity stimuli to notice sensory input (i.e., associated with high neurological threshold and passive self-regulation). The s*ensation seeking* corresponds to the pleasure from rich sensory environments (i.e., associated with high neurological threshold and active self-regulation). The s*ensory sensitivity* relates to the distractibility and discomfort with sensory sensation (i.e., associated with low neurological threshold and passive self-regulation). The s*ensation avoiding* refers to deliberate acts to reduce or prevent exposure to sensory stimuli (i.e., associated with low neurological threshold and active self-regulation).

Furthermore, *neurological threshold* and *behavioral responses* components are calculated separately by the combination of two quadrants: the *high threshold* component combines "low registration" and "sensation seeking" items (i.e., refer to an individual's lack of response or need for more intense sensory stimuli), the *low threshold* component combines "sensory sensitivity" and "sensation avoiding" items (i.e., refer to a person's notice of or annoyance with sensory stimuli), the *passive behavior* component combines "sensory sensitivity" and "low registration" (i.e., refer to an individual's tendency to respond in accordance with his or her neurological threshold), and the *active behavior* component combines "sensations avoiding" and "sensation seeking" (i.e., refer to a person's tendency to respond, to counteract his or her neurological threshold).

Validity and reliability of the questionnaire have been empirically supported by expert judgments, alpha coefficients, factor analysis, and psychophysiological measurements in healthy adults [29]. Because of the presumed role of the insular cortex in visceral processing, we added an additional sensory processing category of "visceral sensation" composed of 12 new questions. The validity and reliability of these items have not been tested by a control sample, but the average of inter-item correlation (0.17) and Cronbach's alpha value (0.7) in our total sample were acceptable. These data are presented as supplementary material (Supplemental Table S1). They were analyzed separately.

Statistical analyses

Between-group differences on basic demographic- and surgery-related variables were tested using a series of analyses of variance (ANOVAs) for continuous variables (age at the time of testing, of surgery, and of diagnosis, time elapsed since surgery, and years of education) and nonparametric Chi-square tests for categorical variables (gender, seizure control outcome, hemisphere of the resection). The level of seizure control outcome was based on the Engel's classification (Engel scores of 1-2 and 3-4 grouped together) [30].

Scores on the AASP quadrants ("low registration," "sensation seeking," "sensory sensitive," and "sensation avoiding") were examined using a series of one-way ANOVA between insular, temporal, and control groups. To respond more specifically to our hypothesis, multiple contrast analyses were performed to compare each group into each quadrant separately when a significant effect was found to determine which group causes the difference. We applied a Bonferroni correction to correct for multiple contrasts analyses by dividing the alpha criterion by the number of comparisons within each quadrant. Thus, differences between groups were considered statistically significant at $p < 0.017$. Two supplementary repeated measures analysis of variance (RM-ANOVA) were conducted to

explore profile differences between groups across interaction effects, with quadrant ("low registration," "sensation seeking," "sensory sensitive," and "sensation avoiding") as the within-subject factor and group (insular vs. temporal vs. control group) as the between-subject factor.

Furthermore, a series of one-way ANOVA was conducted on the components of the neurological threshold (low and high) and behavioral responses (active and passive) between temporal, insular, and control group. Based on the evaluation grids of the AASP manual concerning the quadrants scores, which ones help summarize both of these components scores into each sensory processing category separately (i.e., taste/smell, movement, visual touch, activity level, and auditory processes) [27], a similar series of one-way ANOVA was performed on the components of the neurological threshold and behavioral responses between groups for each sensory processing category separately. Bonferroni post-hoc analyses were performed when significant effects were found.

The visceral modality was examined using a one-way ANOVAs on the total score of items related to visceral function x groups (temporal vs. insular vs. control group).

All analyses were carried out using STATISTICA 12 software (Stat Soft, OK, US), and differences were considered significant at $p < 0.05$.

Results

Sample characteristics

Table 1 reports demographic characteristics and epilepsy surgery information for our insular group. Nonparametric chi-square tests showed a significant difference between both clinical groups concerning the hemisphere resected (χ^2 (1) = 4.93, p = 0.026) (Insular: left = 4 (23.5%), right = 13 (76.5%); Temporal: left = 13 (59.1%), right = 9 (40.9%)). However, insular and temporal groups were

comparable on seizure control outcomes (χ^2 (1) = 0.02, p = 0.88), and on age at the time of surgery, of diagnosis, and time elapsed since surgery (F (1, 37) < 0.09, ps > 0.18). Both patient groups and healthy controls did not differ on age at the time of testing, years of education (F (2, 65)s < 0.89, ps > 0.11), or gender (χ^2 (2) = 1.19, p = 0.55).

AASP questionnaire

Analysis of quadrants

Total of quadrants raw scores (i.e., "low registration," "sensation seeking," "sensory sensitivity," and "sensation avoiding") obtained in the three groups (insular, temporal, and control group) are presented in Table 2. The series of one-way ANOVA on the quadrants showed a significant difference between groups on the "sensation seeking" quadrant (F (2, 65) = 5.91, p = 0.004). Significant contrasts were found between temporal and control groups (F (1, 65) = 10.16, p = 0.002), and between insular and controls (F (1, 65) = 6.02, p = 0.017), suggesting lower scores in both patient groups compared to controls. No difference was found between the temporal and insular groups on this quadrant (F (1, 65) = 0.22, p = 0.64). Comparisons on the other quadrants revealed no other significant group difference (ps > 0.5). RM-ANOVA on the quadrants x group (insular vs temporal vs control group) showed a significant interaction between group and quadrants (F (6, 195) = 2.21, p = 0.043). This interaction was solely attributable to the aforementioned difference between groups on the "sensation seeking" quadrant, with lower scores in both patients groups compared with the control group.

Tableau 2. – Raw scores (mean ± SD) for the four quadrants in the temporal, insular, and control groups

QUADRANTS	Insular (n = 17)	Temporal (n = 22)	Controls (n = 29)
Low registration	30.5 ±7.8	31.5 ± 10.7	29.4 ± 8.8
Sensation seeking	44.1 ± 7.7	42.9 ± 8.6	49.7 ± 6.6
Sensory sensitivity	33.9 ± 9.6	30.6 ± 9.5	33.7 ± 10.4
Sensation avoiding	30.9 ± 10.2	30.9 ± 8.4	33.5 ± 8.8

Analysis of components

The raw scores on components are presented in Table 3. The series of one-way ANOVA on the components of neurological threshold and behavioral responses revealed a significant difference on the "active behavioral responses" component between the three groups (F (2, 52) = 4.41, p = 0.017). A post-hoc analysis revealed a significant difference between temporal and control groups (p = 0.014), with a lower score on the "active behavior responses" component in temporal patients. One-way ANOVA on the component scores for each sensory processing category separately (i.e., taste/smell, movement, visual, touch, activity level, and auditory processes) revealed a significant difference on the raw score of the "active behavioral responses" in the taste/smell modality between groups (F (2, 60) = 5.54, p = 0.006). The post-hoc analysis showed a significant difference between insular and control groups (p = 0.01), with the lowest score in insular patients and the highest in controls. There was no significant difference between temporal and insular groups (p = 0.99), and between temporal and control groups (p = 0.05). For more details, see Table 3.

Tableau 3. – Raw scores (mean ± SD) on the four components (with the sensory processing categories) in the temporal, insular, and control groups

COMPONENTS	Insular (n = 17)	Temporal (n = 22)	Controls (n = 29)
Low Neurological Threshold	68.7 ± 19.5	61.8 ± 17.1	66.8 ± 17.0
Taste/Smell	7.4 ± 3.1	6.7 ± 3.1	7.8 ± 2.8
Movement	7.7 ± 2.7	6.5 ± 2.7	7.6 ± 2.2
Visual	13.8 ± 4.4	12.1 ± 5.1	13.2 ± 5.0
Touch	13.6 ± 5.8	12.3 ± 3.9	15.0 ± 5.2
Activity Level	10.2 ± 2.8	9.6 ± 2.7	9.9 ± 2.8
Audition	14.9 ± 4.4	14.7 ± 5.1	15.0 ± 5.7
High Neurological Threshold	76.2 ± 11.1	73.5 ± 15.9	81.0 ± 8.7
Taste/Smell	12.4 ± 3.5	13.1 ± 3.8	14.6 ± 2.5
Movement	12.0 ± 2.4	10.8 ± 2.8	11.6 ± 2.0
Visual	9.1 ± 2.9	9.1 ± 2.6	9.4 ± 2.2
Touch	15.9 ± 4.3	13.5 ± 3.6	15.1 ± 2.9
Activity Level	15.7 ± 3.3	15.2 ± 2.3	16.0 ± 2.9
Audition	11.5 ± 2.7	12.9 ± 4.6	13.6 ± 2.7
Active Behavioral Responses	78.5 ± 13.2	73.7 ± 13.1	84.6 ± 10.8
Taste/Smell	12.9 ± 3.1	13.7 ± 3.4	15.9 ± 2.7
Movement	9.2 ± 1.6	8.2 ± 1.5	8.8 ± 1.5
Visual	12.0 ± 3.5	10.7 ± 3.1	12.6 ± 2.4
Touch	15.6 ± 4.9	13.1 ± 3.4	16.3 ± 2.8
Activity Level	15.7 ± 2.7	15.4 ± 2.8	17.0 ± 2.8
Audition	12.2 ± 3.5	12.9 ± 4.3	13.9 ± 3.5
Passive Behavioral Responses	66.5 ± 15.8	60.8 ± 19.4	62.9 ± 15.1
Taste/Smell	6.8 ± 2.9	6.0 ± 2.5	6.5 ± 2.2
Movement	10.3 ± 3.8	9.0 ± 4.1	10.1 ± 3.0
Visual	10.5 ± 3.8	10.3 ± 4.3	10.4 ± 3.2
Touch	14.0 ± 4.1	12.4 ± 4.9	13.9 ± 5.2
Activity Level	10.2 ± 3.5	9.5 ± 4.2	9.0 ± 3.4
Audition	14.3 ± 3.8	14.7 ± 5.6	14.6 ± 4.7

Supplementary analyses

Because of the fact that a significant difference was observed between both clinical groups concerning the hemisphere resected (p = 0.026), we conducted two additional analyses of covariance (ANCOVAs) adjusted for the side of resection (i.e., the covariate). After checking for the side of resection, the differences previously reported between groups remained significant on the quadrant and component variables (p < 0.005).

Visceral processing items analysis

The one-way ANOVA on the score of visceral sensation with our three groups (i.e., temporal vs. insular vs. control group) did not show a significant difference (F (2, 65) = 2.51, p = 0.09). Our control group showed the highest total score on visceral function items.

Tableau 4. – Supplemental Table S1. Validity and reliability summary of the items related to visceral function added to the AASP questionnaire

	Mean of the raw score	**SD**	**Average inter-item correlation**	**Cronbach's alpha**
	28.0	**7.4**	**0.18**	**0.70**
VISCERAL FUNCTION ITEMS	***Means if deleted***	***SD if deleted***	***Item-total correlation***	***Alpha if deleted***
I forget to eat because I am not hungry.	25.9	6.8	0.32	0.69
I take part into activities which provide me strong sensations.	25.4	7.1	0.08	0.72
During the winter, I avoid going outside when it is cold.	25.6	6.6	0.47	0.67
I avoid certain foods which give me stomach burns.	25.7	6.5	0.52	0.66
I need to go to the toilet even though I just went.	25.7	6.9	0.27	0.70
I eat between meals because I am too hungry.	25.4	6.8	0.31	0.69
During the summer, I try to enjoy the heat.	24.9	6.9	0.22	0.71
I am disturbed by my own internal sensations.	26.1	6.8	0.42	0.68
I must go to the toilet urgently because I haven't notice I had to go before.	26.2	6.7	0.64	0.65
I feel like I am in someone else's body.	26.6	7.1	0.25	0.70
I do not feel satiety after eating.	26.0	6.7	0.44	0.67
I get shivers when I'm cold.	24.4	6.9	0.23	0.70

Discussion

This study examined sensory information processing using the self-administered AASP questionnaire in patients who underwent resection of the insular cortex. Our results suggest that insular and temporal resections in patients with drug-refractory epilepsy are associated with a low "sensation seeking" behavior, reflecting a lack of exploration or engagement with sensory inputs from the environment. Furthermore, an impairment in the "active behavioral responses" for the gustatory/olfactory sensory processing is also reported in patients who underwent an insular resection.

The "sensation seeking" quadrant measures active behavioral responses associated with a high neurological threshold by enjoyed and creative experiences in daily life and by the pursuit of sensory stimuli [27]. Several studies have reported that individuals with temporal lobe epilepsy, especially those with depressive symptoms, exhibit considerably less need for sensory stimulation and novelty-seeking and that temporal lobe epilepsy surgery is associated with an enhanced introverted social personality [31, 32]. Furthermore, the insular cortex is a multimodal structure involved in the integration of sensory inputs and plays a central role in the "salience network" in detecting and distributing sensory information to higher order cognitive structures [33]. The low scores in "sensation seeking" behaviors in both resection groups suggest that patients with insular and temporal epilepsy surgery are not actively involved in intensifying the sensory environment. The lack of active exploration behaviors shown in insular and temporal resection groups may reflect habits to prevent and avoid situations in which the risk of precipitating epileptic seizures increases or this may also suggest an alternation in novelty-seeking by the difficulty to detect sensory salient information in the case of insular resection.

The insular cortex is involved in processing the intensity, quality, and affective value of taste stimuli. Furthermore, the insula is consistently activated by olfactory stimuli in functional neuroimaging studies [22, 34, 35]. Thus, the primary taste cortex, which requires gustatory, olfactory, and visceral sensory inputs for taste representation and perception of flavor, is located in the mid-insular cortex [36]. The significant difference between insular and control groups in taste/smell sensory processing in the "active behavioral responses" component is in accordance with the role of the insula in gustatory/olfactory processing, suggesting that insular resection may be associated with impairments in gustatory/olfactory processing as previously documented by lesion studies [17, 19]. As suggested by these studies and supported by our present findings, insular resection may be associated with increased sensitivity to these types of sensory stimuli, reflected by a lower sensory threshold or reduced need for intense sensory input.

Given the evidence linking insular responses to auditory information processing [15, 16, 20, 37], it is somewhat surprising that insular resections were not associated with self-reported impairments in the auditory modality. Furthermore, the insular cortex is thought to be involved in the meta-representation of the state of the body based on input from visceral afferent pathways projecting the information caudo-rostrally to create the subjective awareness of interoceptive representations [1, 4]. However, we did not find any impairments in visceral sensation behavior in our insular resection group.

It is important to consider some limitations in the present study. First, because of the low incidence of the insular epilepsy surgeries, our insular sample is relatively modest. A larger group would have permitted comparisons according to specific insular subregions resected. As suggested by direct electro-cortical stimulation studies, specific insular subregion stimulation provokes precise sensory responses [9, 10]. Therefore, based on our results alone, we cannot conclusively establish if

there is a link between impairments and specific insular subregions. Furthermore, most of the resections were not purely insular as they often included the adjacent operculum and temporal structures. The other resected structures in some of our patients with insular epilepsy include the amygdala, hippocampus, frontal operculum, and orbitofrontal cortex, which might contribute to the observed alterations in sensory processing, especially for olfactory and gustatory modalities [34]. Thus, we cannot exclude that our findings highlight cortical and subcortical networks alterations in which the insular cortex contributes rather than a specific role of this structure in these sensory processes. Additionally, the AASP questionnaire may not be sensitive enough to detect subtle sensory disturbances in patients who are less demonstrative of their symptoms. Furthermore, it is important to consider that the assessment was a retrospective self-reported questionnaire. Pre-and post-surgery sensory assessments would have been better to objectify changes associated with insular resection as some impairments may be present prior to surgery.

Conclusion

To our knowledge, this study is the first to assess sensory processes changes in a group of patients with epilepsy surgery who underwent insular resection for drug-resistant epilepsy. Our findings provide preliminary evidence that insular resections are associated with relatively mild to moderate impairments in sensory processing, especially in the sensation-seeking and active behavioral responses in the taste/smell modality. These impairments support the notion that the insula plays an active role in sensory processing. Before performing insular epilepsy surgery, these potential postoperative disturbances should be discussed and explained to the patients. However, the relatively mild impairments in our sample of insular patients do not constitute a contraindication for insular resections in the context of epilepsy surgery, especially among patients with drug-resistant

and disabling seizures. Obviously, further investigation with a larger and more homogeneous sample is needed.

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ARTICLE IV

THE EFFECTS OF INSULAR AND MESIO-TEMPORAL LESIONS ON AFFECTIVE INFORMATION PROCESSING: PRELIMINARY EVIDENCE FROM PATIENTS WITH EPILEPSY SURGERY.

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Abstract

Depressive symptoms and anxiety are common complaints in patients who have had epilepsy surgery. Recent studies have reported disturbances in emotional memory, facial and vocal emotion recognition, and affective learning after temporal lobe and/or insular resection for drug-resistant seizures, suggesting that these regions may be involved in emotional processes underlying psychological symptoms. The insula is a core component of the salience network and is thought to be involved in processing emotions such as disgust, and the role of mesial temporal lobe structures in affective processing is well established. However, to our knowledge, no study has yet investigated whether attentional processing of affective information is altered when these structures are resected as part of an epilepsy surgery. The present study examines the interference control capacity and attentional biases for emotional information in adult epileptic patients who underwent temporal lobe resections including the amygdala and hippocampus (*n* = 15) and/or partial or complete insular resections (*n* = 16). Patients were tested on an Emotional Stroop test and on a Dot-Probe task using fearful and disgusting pictures and were compared with a healthy control group (*n* = 30) matched for age, gender, and education. Repeated-measures analyses of variances revealed a significant effect of emotional words on color naming speed in the Emotional Stroop task among insular patients, which was not observed in the other groups. By contrast, the groups did not differ on Dot-Probe task performance. These preliminary findings suggest that insular damage may alter emotional interference control.

Keywords: Insula; Epilepsy; Emotional Stroop; Interference; Attention; Dot-Probe Task

Introduction

Several studies have documented a strong relationship between epilepsy and psychiatric disorders such as depression and anxiety disorders (AD). It has been suggested that epilepsy may promote the development of these disorders through the uncertainty and unpredictability of seizures, chronic stress exposure, and restriction on living normal activities resulting in low self-esteem, social rejection, and stigmatization [1,2]. More specifically, depression and anxiety have been reported as the most frequent psychiatric disorders in patients with temporal lobe epilepsy (TLE) and are associated with a reduced quality of life [3,4]. The higher propensity to develop psychiatric disorders in patients with TLE is thought to be attributable to the role of mesial temporal lobe structures in emotion, mood, and behavioral regulation [5–7]. TLE, major depressive disorders (MDD), and AD involve common structures (e.g., amygdala, hippocampus, lateral temporal lobe, and temporal pole) [1,8–10]. Furthermore, neuroimaging studies have reported hippocampal sclerosis, amygdala atrophy, and functional connectivity alterations within the default mode network (DMN) in patients with TLE [11–17], while similar structural and connectivity alterations have been shown in patients with MDD and AD [18–21].

Several studies have reported affective processing disturbances in patients with TLE or following resection of temporal lobe structures (e.g., amygdala and hippocampus) as part of TLE surgery, such as impaired emotional memory and perception [22], facial and vocal emotion recognition [23–27], and attentional processing of emotional information [28,29]. Furthermore, studies have showed an increased risk for new-onset or persistent MDD and/or AD following partial or complete temporal lobe resection [30–32]. According to Wrench and colleagues [33], temporal lobe surgery in the left hemisphere is associated with increased risk of persisting emotional disorders, the severity of which is related to the extent of mesio-temporal structures resection.

The insular cortex is an uncommon epileptogenic location from which seizure activity may mimic that of TLE [34]. Since insular lobe epilepsy (ILE) is rare and much less extensively studied than TLE, few studies have investigated mood disorders in patients with ILE [35], but several works have showed structural and functional connectivity abnormalities in the insula in patients with MDD and AD [18,19]. The insula plays a central role in the "salience network", along with the dorsal anterior cingulate cortex, in switching brain activity from the DMN to central-executive network (CEN) to allow the access to attentional resources for relevant information, such as affective stimuli [36,37]. Unsurprisingly, several neuroimaging studies have reported abnormal insular activity in patients with MDD during emotional and relevant information processing [38–41], and this was associated with the severity of symptoms in MDD [42–44]. Furthermore, insular resection and lesions have been associated with impairments in emotion recognition, especially with the emotion of disgust, and with altered valence and arousal ratings of emotional words and pictures [45–47]. Hébert-Seropian and colleagues [48] have also reported increased irritability, emotional lability, and higher anxiety level as reported by patients' relatives following insular resection. Transient anxiety and mood alterations for 6-8 weeks postsurgery have also been reported [49]. Currently, no standardized neuropsychological test is available to assess affective processing impairments following temporal and insular lobe surgeries in patients with epilepsy. Such neurobehavioral tasks would be useful in this population to bring out potential emotional disorders. The "Emotional Stroop test" is a paradigm aimed to examine impairments in the interference control to emotional information, as reflected by slowing color naming of emotional words (e.g., fear or disgust connotations) in comparison with neutral ones, as has been observed in patients with MDD and AD [50,51]. On the other hand, the "Emotional Dot-Probe paradigm" assesses the deployment of visual attention related to emotional stimuli, by the contribution of bottom-up and top-down processes [52–54]. The bottom-up effect reflects the early

vigilance/avoidance facilitation occurring about 100 ms poststimulus onset, whereas the top-down effect occurs around 500 ms poststimulus and highlights difficulty in disengaging attention [55]. Faster detection to the probe location on the same side as threatening stimuli (i.e., congruent trial) than in the opposite side (i.e., incongruent trial) highlights the vigilance facilitation in bottom-up processing, whereas the difficulty in top-down attention disengagement from threatening stimuli is reflected by longer reaction times (RTs) in incongruent trials relative to congruent ones [29,52,56]. Attentional biases for negative emotional information have been reported in several clinical populations, including MDD, AD, and TLE [28,57]. Such tasks are likely to be sensitive to the effects of insular and temporal lobe resections, given the well-established role of these structures in emotion processing, and more especially disgust for the insula, and fear for the temporal lobe [58,59].

The aim of the present study was to examine attentional biases and interference control related to affective information in patients who had an epilepsy surgery involving the insula and/or mesiotemporal resection. We hypothesized that insular resection would be associated with global impairments in the ability to process affective stimuli, especially with the emotion of disgust, whereas temporal lobe surgery would be specifically associated with impaired fear processing. We also hypothesized that both resection groups would show higher depressive and anxious symptoms than the control group and that these symptoms would be correlated positively with attentional biases and emotional interference.

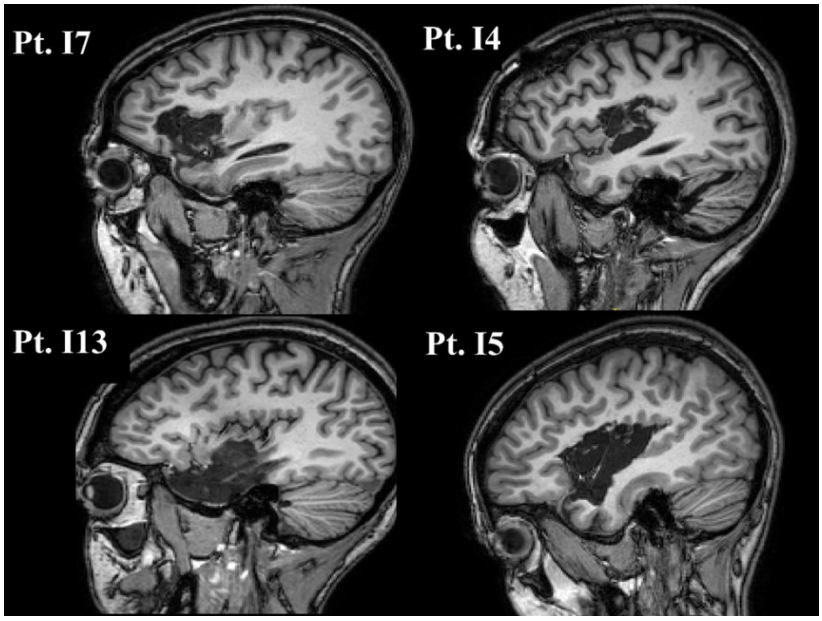
Method and Material

Participants

We recruited 16 adult patients (13 females; mean age = 39.1 years, SD = 5.9) who underwent partial or complete insular resection in our epilepsy center for drug-resistant epilepsy, and 15 patients

(9 females; mean age = 35.3 years, SD = 7.7) who underwent TLE surgery, including amygdalo-hippocampectomy. Two additional temporal patients were excluded after their participation because of invalid performance due to lack of motivation and/or random responding. All patients were tested at least four months after surgery. Patients were invited to perform our neurobehavioral tests following their routine neurological examination at the Centre Hospitalier de l'Université de Montréal (CHUM). A group of 30 adults (19 females; mean age = 36 years, SD = 11.9), matched for gender, age, and education, were recruited using ads on our center's intranet website to form the healthy control group. None of them suffered from neurologic disorders, psychiatric conditions, head trauma, or brain injury. This study was approved by our institutional ethics committee. Figure 1 depicts postsurgery MRIs of the brain of representative cases of the insular group. This study was approved by the CHUM ethics committee.

Figure 1. – T1-weighted MRI of the brain after surgery of representative cases of the insular group. Patient I7: selective resection of the left anterior insula; Patient I4: resection of the right posterior insula and parietal operculum; Patient I13: resection of the right anterior-inferior and posterior-inferior insula, temporal (SAH), and temporal operculum; Patient I5: complete right insulectomy with fronto-parieto-temporal opercular resection.



Neuro-behavioral assessments

Emotional Stroop test

In the Emotional Stroop test, the participant is asked to name the ink color of word stimuli, as fast and as accurately as possible. The task comprises four conditions, each including 60 word stimuli, arranged in six lines on a white card (60 stimuli in each card, 210 x 300 mm). In the first condition (Color naming), "word" stimuli were series of "X"s printed in red, blue, or green (each color occurring 20 times). In the second condition (Neutral words), 15 different "emotionally neutral" words were used, printed in red, blue, or green, each occurring four times. In the third condition (Emotional words), 15 different "emotional" words were used, each also occurring four times. A fourth card (Color-interference naming) was made up of color words (i.e., red, blue, and green) printed in a different ink color. Each word was presented 20 times. The four cards were administered in the same order to each participant and were each preceded by a 10-word practice trial. Completion time and number of errors were computed for each condition.

Neutral and emotional words used in this task are listed in Table 1. Neutral and emotional words were matched for literary frequency (p = 0.86), length (p = 1.00), and grammatical gender (p = 0.52) [60]. Furthermore, prior to the study, a sample of 31 adult participants rated each word for concreteness, "visualizability", arousal, and valence on a 5-point Likert Scale (1 = low; 5 = high). Both sets of word were found to be comparable for concreteness and visualizability, whereas emotional words were rated as significantly more emotionally arousing and negative than neutral words.

Tableau 1. – List and mean ratings of word stimuli used in the Emotional Stroop test

Word stimuli (French)	English translation	Concreteness	Visualisability	Arousal	Valence
Neutral words					
Arbuste	*Bush*	4.71	3.84	1.35	3.39
Coton	*Cotton*	4.61	3.97	1.26	3.13
Farine	*Flour*	4.90	4.26	1.06	3.00
Fonction	*Function*	2.03	2.19	1.42	3.03
Index	*Index finger*	3.65	2.77	1.00	3.03
Liqueur	*Liquor*	4.72	3.84	1.32	3.16
Liste	*List*	3.84	3.71	1.48	3.03
Message	*Message*	-	3.65	2.26	3.32
Principe	*Principle*	1.94	2.84	2.03	3.39
Prochain	*Next*	2.13	1.74	1.65	3.19
Radio	*Radio*	4.71	4.00	1.48	3.45
Rapport	*Report*	3.03	2.77	1.74	3.00
Saison	*Season*	3.61	3.58	2.03	3.35
Sonnerie	*Ringtone*	4.03	2.81	1.84	3.03
Tante	*Aunt*	4.45	3.84	2.29	3.81
Mean (SD)		**3.7 (0.7)**	**3.3 (0.7)**	**1.6 (0.4)**	**3.2 (0.2)**
Emotional words					
Accident	*Accident*	4.03	3.58	3.81	1.32
Cadavre	*Cadaver*	4.26	3.42	3.61	1.19
Cancer	*Cancer*	3.35	2.81	3.81	1.06
Couteau	*Knife*	4.90	4.55	1.61	2.61
Douleur	*Pain*	2.84	2.94	3.87	1.42
Famine	*Famine*	3.48	3.06	3.42	1.23
Honte	*Embarrassment*	2.00	2.71	3.55	1.58
Microbe	*Microbe*	3.42	3.77	1.77	2.16
Prison	*Jail*	4.35	1.97	2.81	1.55
Regret	*Regret*	1.94	1.90	3.39	1.68
Saleté	*Dirt*	4.10	3.77	2.19	2.06
Stress	*Stress*	2.71	2.52	3.94	1.61
Suicide	*Suicide*	3.84	3.00	3.90	1.03
Tueur	*Murderer*	3.71	3.00	3.45	1.06
Violence	*Violence*	3.39	3.26	3.81	1.16
Mean (SD)		**3.5 (0.8)**	**3.1 (0.7)**	**3.3 (0.8)**	**1.5 (0.5)**
***p*-value**		**0.49**	**0.37**	**< 0.0001**	**< 0.0001**

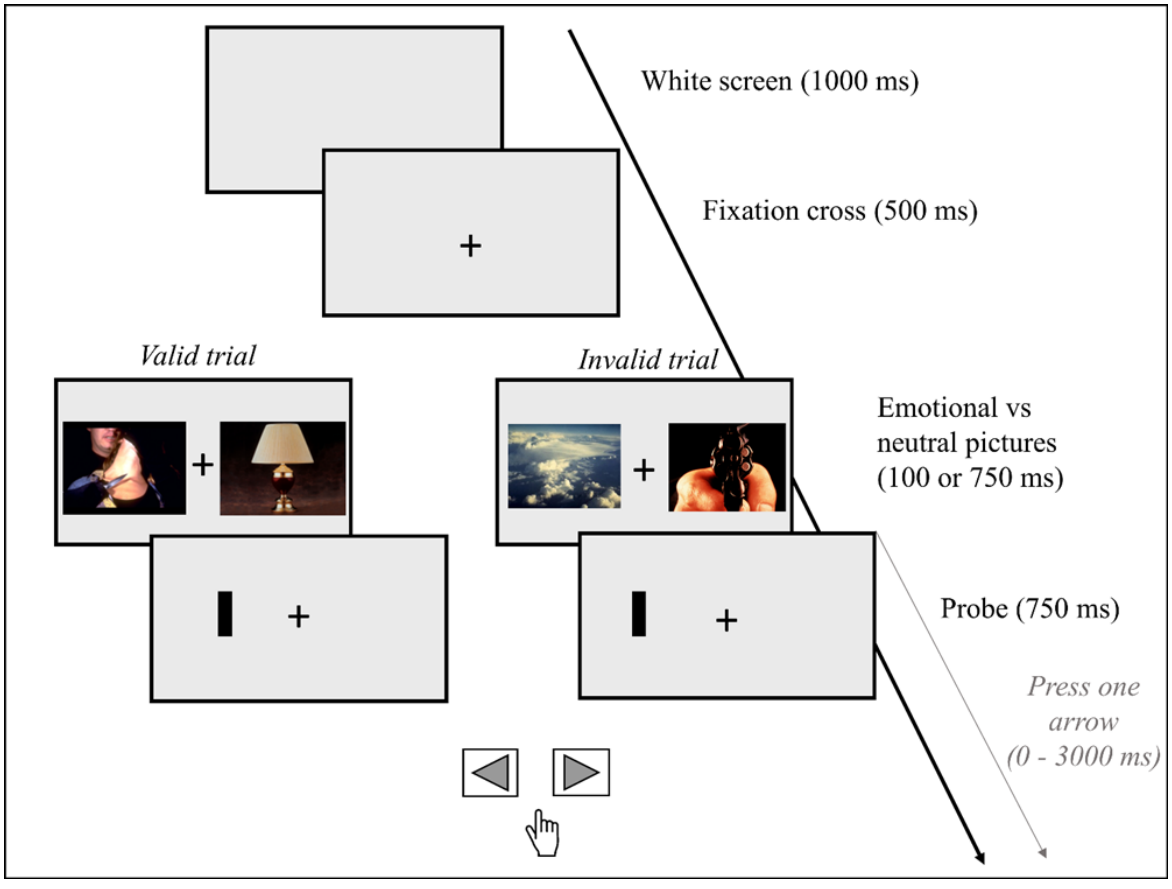
Dot-Probe task

In the Dot-Probe task, the participant sits behind the computer at a distance of approximately 60 cm from the screen and is asked to press the left or the right arrow on the keyboard as fast as possible to indicate the location of the probe. Each trial starts with a white screen for 1,000 ms. Then, a black fixation cross is presented for 500 ms at the center of the screen, followed by a pair of pictures displayed on each side for either 100 ms or 750 ms, at equal distances from the fixation cross of the computer screen. After the offset of the two pictures, a small probe is presented for 750 ms, which appears at the location of one of the two pictures, with an interstimulus interval (ISI) of 100 ms. Responses are recorded between 0 and 3,000 ms after target stimulus onset. Emotional picture position (i.e., left/right), probe congruence (i.e., valid/invalid), presentation duration of pictures (i.e., 100/750 ms) and type of pictures pair (i.e., neutral-emotional/emotional-neutral) were presented equally. A total of 96 trials were presented with after an eight-trial practice. Reaction times and errors were computed. The Dot-Probe task is illustrated in Figure 2. The task was implemented in E-Prime 3.0 Software.

Pictures were selected from the International Affective Picture System (IAPS) [61], a standardized set of emotion eliciting color pictures. Sixty-four images depicting animals, objects, humans, and landscapes of 5 x 5 cm were selected according to the normative ratings of valence (from pleasant to unpleasant) and arousal (from calm to excited) [61]. Images are neutral (n = 32), disgust (n = 16), and fear (n = 16) pictures selected according to their mean arousal and valence in a 9-point rating scale such that 1 represents a low pleasure and a low arousal, and 9 represents a high pleasure and a high arousal. A series of *t* tests compared valence (disgust: 1.85 ± 0.37; fear: 2.09 ± 0.39; neutral: 5.19 ± 0.56) and arousal (disgust: 6.73 ± 0.54; fear: 6.75 ± 0.37; neutral: 3.21 ± 0.65) ratings within each specific emotion category. Both the disgust and fear pictures were similar on mean valence (p =

0.08) and arousal (p = 0.91) but were significantly different from neutral pictures (p < 0.0001). Each picture was presented four times. The practice set contained 8 neutral pictures presented twice. The order of trials was randomized for each participant.

Figure 2. – Illustration of the Dot-Probe task. Examples of valid (left side) and invalid (right side) trials sequences. Following a fixation cross for 500 ms, emotional pictures are presented simultaneously for either 100 or 750 ms. RTs are measured from the onset of the probe which followed the pictures until the arrow on the keyboard is pressed. Note that stimuli are not to scale.



Supplementary measures

Participants additionally completed two self-reported questionnaires to assess trait anxiety and depressive symptoms: (1) the State-Trait Anxiety Inventory Trait (STAI-Y; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) (20 items; scores ranging from 20 to 80); (2) the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) (21 items; scores ranging from 0 to 63).

Statistical analyses

Between-group differences on basic demographic and surgery-related variables were tested using a series of analyses of variances (ANOVAs) for continuous variables (age at the time of testing, of surgery, and of diagnosis, time elapsed since surgery, and years of education) and nonparametric Chi-square tests for categorical variables (gender, seizure control outcome, hemisphere resected).

Performance (RTs and number of errors) in the Emotional Stroop task was examined using a 3 x 4 repeated-measures analysis of variance (RM-ANOVA) with group (insular vs. temporal vs. control group) as the between-subject factor and condition (Color naming, Neutral words, Emotional words, and Color-interference naming) as the within-subject factor. To respond more specifically to our hypothesis, a second 3 x 2 RM-ANOVA was performed with group as the between-subject factor (insular vs. temporal vs. control group) and condition (Neutral words vs. Emotional words) as the within-subject factor. Dot-Probe task performance (RTs and number of errors) was examined using a 3 x 2 x 2 x 2 RM-ANOVA with group (insular vs. temporal vs. control group) as the between-subject factor, and with presentation duration (100 vs. 750), probe congruence (valid vs. invalid), and emotion (disgust vs. fear) as the three within-subject factors.

The associations between BDI and STAI scores, performance on the Emotional words condition for the Emotional Stroop test, and attentional biases toward disgust and fear pictures for the Dot-

Probe task in patients with insular and temporal lobe resection, were examined using Spearman correlations.

All analyses were performed using STATISTICA 12 software (Stat Soft, OK, US), and differences were considered significant at $p < 0.05$. One subject of the control group was excluded from the Emotional Stroop task analyses due to a stopwatch problem and the data backups crashed for two patients in the Dot-Probe task.

Results

Sample characteristics

Socioemotional characteristics and epilepsy surgery information for each patient are presented in Table 2. Insular and temporal patients did not differ on age of surgery and of diagnosis, and time elapsed since surgery (F (1, 29)s < 0.15, ps > 0.33). Age at the time of testing and years of education were comparable between both clinical groups and healthy controls (F (2, 58)s < 0.52, ps > 0.28). Nonparametric Chi-square tests did not show any significant difference between our clinical groups concerning the hemisphere resected (χ^2 (1) = 1.6, p = 0.21), gender (χ^2 (1) = 1.7, p = 0.19), and seizure control outcome (χ^2 (3) = 3.8, p = 0.28). There were no significant differences in the BDI depression score (mean ± SD: insular group = 10.9 ± 8.9; temporal = 12.9 ± 10.3; control = 6.6 ± 10.0, F (2, 58) = 2.32, p = 0.11) and the STAI anxiety score (mean ± SD: insular group = 38.3 ± 8.7; temporal = 39.7 ± 11.8; control = 34.6 ± 12.5, F (2, 58) = 1.16, p = 0.32). Correlations between BDI and STAI scores, and with performance on Emotional Stroop test and Dot-Probe task, were not significant (ps > 0.10).

Tableau 2. – Demographic and surgery-related characteristics of both groups with resection

Pt.	Sex	Education (y)	Time since surgery (y)	Age at surgery (y)	Location of surgery				Engel's classification of outcome
					Side	Insular area	Temporal area	Other areas	
Insular group									
I1	f	11	2.0	34	R	Inferior	SAH	T op	III
I2	f	13	0.9	30	R	Anterior	SAH	T op	I
I3	f	15	6.0	35	R	Posterior	-	T-P op	IV
I4	f	12	5.8	32	R	Radical	-	P op	I
I5	f	16	6.2	23	R	Radical	-	F-T-P op	III
I6	f	16	7.0	27	R	Anterior	-	OFC	I
I7	f	12	6.2	38	L	Anterior	-	F-T op	I
I8	m	14	7.1	37	R	Anterior-superior	-	F op	I
I9	f	11	4.7	33	L	Anterior-superior	-	F op	I
I10	f	7	14.3	23	R	Anterior	ATL	T op	I
I11	f	8	1.0	49	L	Anterior	-	-	I
I12	m	12	2.3	32	L	Anterior	-	OFC	I
I13	f	14	12.7	26	R	Anterior-inferior & posterior-inferior	SAH	T op	I
I14	f	18	2.0	32	L	Radical	ATL	T op	III
I15	f	13	9.7	39	L	Radical	ATL	T op	III
I16	m	13	3.6	33	R	Anterior-inferior	ATL	T op	I
Mean	-	**12.8**	**5.7**	**32.7**	-	-	-	-	-
Temporal group									
T1	m	16	3.6	26	L	-	ATL	-	IV
T2	f	12	4.0	36	L	-	ATL	-	I
T3	f	11	1.5	44	R	-	ATL	-	I
T4	m	14	8.9	34	L	-	SAH	-	I
T5	m	7	2.0	33	L	-	ATL	-	I
T6	f	14	3.0	29	R	-	ATL	-	I
T7	f	14	4.4	30	R	-	ATL	-	I
T8	m	8	7.9	19	R	-	ATL	-	I
T9	f	11	6.1	43	R	-	SAH	-	I
T10	f	11	3.4	26	L	-	ATL	-	III

T11	f	16	5.0	23	L	-	ATL	-	I
T12	f	16	3.8	24	R	-	ATL	-	I
T13	f	8	0.4	39	L	-	ATL	-	I
T14	m	13	3.6	19	L	-	ATL	-	II
T15	m	13	10.1	32	L	-	ATL	-	I
Mean	-	**12.3**	**4.5**	**30.5**	-	-	-	-	-
***p*-value**	**0.19**	**0.60**	**0.34**	**0.40**	**0.21**	-	-	-	**0.28**

Abbreviations: ATL = anterior temporal lobe; f = female; F = frontal; L = left; m = male; OFC = orbitofrontal cortex; op = operculum; P = parietal; R = right; SAH = selective amygdalo-hippocampectomy; T = temporal

Emotional Stroop test

Mean completion times for the Emotional Stroop test are reported in Table 3. Using the Greenhouse-Geisser correction for violation of sphericity, RM-ANOVA on completion times showed a significant effect of condition (F (1.73, 98.6) = 171.67, p < 0.001) (mean completion times of conditions: 1 < 2 < 3 < 4). There was no significant interaction between group x condition (all four conditions) (F (3.46, 98.6) = 0.30, p = 0.89). Results from our second RM-ANOVA did not show a significant effect of condition (Neutral words vs. Emotional words) (F (1, 57) = 2.05, p = 0.16) and there was no significant interaction between group x condition (F (1, 57) = 1.30, p = 0.28). To respond more specifically to our hypothesis, we performed three independent simple effects tests between neutral and emotional words conditions with our three groups. The insular group showed a significant difference between neutral and emotional words conditions (F (1, 57) = 4.16, p < 0.05) (see Figure 3), which was not found in the temporal (p = 0.96) and control (p = 0.76) groups. Exploratory analyses involving only the insular and the temporal groups showed a significant interaction between both clinical groups and condition (Neutral words vs. Emotional words) (F (1, 29) = 5.39, p = 0.01), suggesting a significantly larger effect of emotion on color naming in the insula group in comparison to the temporal group. Exploratory analyses with the hemisphere as the between-subject factor revealed no significant main effect (F (1, 29) = 2.04, p = 0.16) nor interaction (F (3, 87) = 2.26, p = 0.09) of side of resection.

There was no significant group difference in the number of errors in the four conditions (Mean ± SD: insular group = 0.64 ± 1.3; temporal group = 0.75 ± 1.1; control group = 0.83 ± 1.3; ps > 10).

Figure 3. – Mean completion times in the Stroop task between neutral-word and emotional-word color naming conditions. Error bars represent standard deviations. The star indicates significant difference in completion times between both conditions in the insular group ($p < 0.05$).

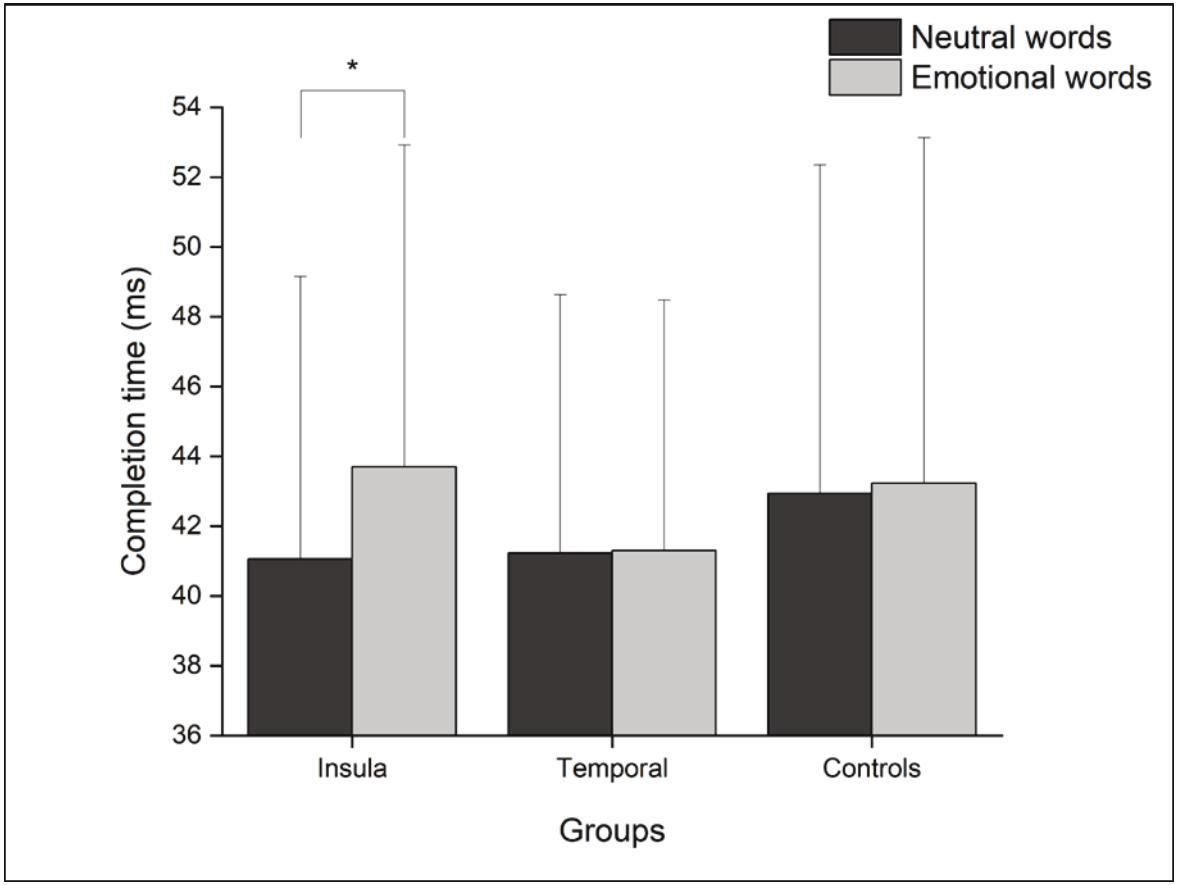


Tableau 3. – Mean (± SD) completion times (ms) for each condition in the Stroop task

	Insular group (n=16)	*Temporal group (n=15)*	*Healthy controls (n=29)*
Color naming	36.3 (± 5.4)	36.5 (± 6.2)	37.3 (± 6.3)
Neutral-word color naming	41.1 (± 8.1)	41.2 (± 7.4)	42.9 (± 9.4)
Emotional-word color naming	43.7 (± 9.2)	41.3 (± 7.2)	43.2 (± 9.9)
Color-interference naming [a]	59.0 (± 19.5)	59.9 (± 11.1)	60.6 (± 12.3)

[a] Violation of sphericity was corrected using the Greenhouse-Geisser in our global RM-ANOVA.

Dot-Probe task

Mean RTs for the Dot-Probe task are reported in Table 4. Results from RM-ANOVAs on RTs showed significant main effects of presentation duration (F (1, 56) = 4.99, p = 0.03) and emotion (F (1, 56) = 5.08, p = 0.03) factors. All groups responded faster to probes presented for 750 ms compared to 100 ms and had shorter RTs for fearful compared to disgusting pictures. There was a significant interaction between congruence x emotion x presentation duration x group factors (F (2, 56) = 3.44, p = 0.04). A trend for interaction between group factor and congruence (valid) x emotion (fear) x presentation duration (100 vs. 750) was found (fixed-levels) (F (2, 56) = 3.46, p = 0.07). In the control group, this contrast was significant (F (1, 56) = 12.4, p < 0.001): on valid fear trials, the control group was faster for 750 ms presentation duration than to 100 ms. This contrast was not significant in insular (p = 0.91) and temporal groups (p = 0.56). A second significant contrast was found in the control group for congruence (invalid) x emotion (disgust) x presentation duration (100 vs. 750) (F (1, 56) = 6.28, p = 0.02). On invalid disgust trials, the control group was faster for 750 ms presentation duration than for 100 ms while similar RTs for 100 and 750 ms presentation duration were showed in insular (p = 0.86) and temporal groups (p = 0.99). However, there was not significant interaction between group

factor and these previous fixed levels of factors (F (2, 56) = 0.99, p = 0.32). Exploratory analyses with the hemisphere as the between-subject factor revealed no significant main effect (F (1, 27) = 0.18, p = 0.67) nor interactions (F (1, 27)s < 1.5, ps > 0.24) of side of resection.

Repeated-measures ANOVAs on number of errors for the Dot-Probe task showed a significant interaction between presentation duration and emotion (F (1, 56) = 5.6, p = 0.02) such that more errors were made at 100 ms for disgust emotion compared with 750 ms and at 750 ms for fear compared to 100 ms. Another significant interaction was found between emotion and group (F (2, 56) = 4.14, p = 0.02). More specifically, a significant contrast showed an interaction effect with group (insular vs. temporal and control) and emotion (fear vs. disgust) (F (1, 56) = 8.13, p = 0.01). The insular group made less errors with fear emotion than disgust, whereas temporal and control groups showed less errors with disgust emotion than fear. However, percentage of errors remained low in all groups (Mean ± SD: insular group = 0.34% ± 0.96; temporal group = 0.69% ± 1.7; control group = 0.56% ± 1.6).

Tableau 4. – Mean (± SD) RTs for each condition in the Dot-Probe task (presentation duration x emotion x congruence)

Presentation duration (ms)	**100**				**750**			
Emotion	**Fear**		**Disgust**		**Fear**		**Disgust**	
Congruence	**Valid**	**Invalid**	**Valid**	**Invalid**	**Valid**	**Invalid**	**Valid**	**Invalid**
Insular group (n=15)	558 (± 122)	557.4 (± 127)	562.2 (± 137)	556.8 (± 134)	558.9 (± 128)	548.8 (± 119)	549.1 (± 121)	558.9 (± 131)
Temporal group (n=14)	470.2 (± 83)	484.8 (± 85)	479.4 (± 107)	483.5 (± 86)	465.1 (± 83)	474.1 (± 97)	473.3 (± 85)	483.3 (± 95)
Healthy controls (n=30)	505.5 (± 90)	498.3 (± 91)	504.7 (± 96)	514.9 (± 110)	484.3 (± 104)	492.8 (± 103)	493.9 (± 105)	494.7 (± 100)

Discussion

This study examined interference control capacity and attentional biases for emotional information in patients who underwent resection of the insular cortex and/or mesio-temporal structures as part of epilepsy surgery. Insular resection was associated with mild disturbance in emotional interference control, as reflected by slower completion time for naming emotional words color compared with neutrals on an Emotional Stroop task. By contrast, no clear effect of epilepsy surgeries was found on attentional biases for emotional information, as assessed by a Dot-Probe task employing affective pictures.

To our knowledge, this study is the first to report emotional interference control impairment on an emotional Stroop task in a group of patients with lesions to the insular cortex. Such disturbance in emotion information processing and mood alterations in these patients is not surprising; the insula is thought to play a crucial role in the "salience network" by modulating affective information [45]. Using similar emotional Stroop paradigms, several studies have reported slower completion times for naming the color of words with negative emotional valence compared to neutral words in patients with MDD, dysphoric symptoms, and AD. However, weak emotional interference control capacity in the insular group cannot be solely explained by mood, as there were no significant correlations between Emotional Stroop task performance and self-reported depression and anxiety symptoms, nor any difference in depressive and anxiety symptoms between the insular and the other groups.

Hung and colleagues [62] have reported three dimensions of inhibitory processes, i.e., cognitive inhibition (i.e., suppression of competing cognitive processing), response inhibition (i.e., suppression of preponderant responses), and emotional interference (i.e., suppression of distractive emotional information). Although these three dimensions are sustained by distinct neural networks, the anterior insula appears to be a common substrate for all these inhibitory dimensions. More

specifically, the insula has been associated with goal-directed attention [63,64], error awareness [65], and resolution of interference [66–69]. Our results with the Emotional Stroop test support an involvement of the insula in emotional interference control, but not in other inhibitory dimensions, as insular patients did not differ from other groups in "classic" Stroop color-word interference performance. This is consistent with previous findings from our group showing no difference in "classic" Stroop color-word interference performance before and after epilepsy surgery that included resection of the insula [70].

In the Dot-Probe task, all groups showed faster RTs for detecting the probe in trials with fearful compared with disgusting pictures, independently of the congruence and presentation duration. As suggested by LeDoux [71], fear-related information is treated as a priority content for our survival, reflected by an attentional deployment. Although several studies have reported impairments in fear recognition following a temporal lobe resection [59], our temporal group showed RTs with fear-related pictures comparable with those of the insular and control groups ($ps > 0.53$). In the same vein, although several studies have suggested a specific role of the insula in disgust emotional processing [58,72–74], we did not find such disgust-related impairments in our insular group ($ps > 0.74$). However, other studies suggest that the involvement of the insula in affective picture processing depends on emotional arousal rather than emotional valence or specific emotions [45,75]. Although the insular group showed less errors in trials with fear emotional pictures than disgust, we cannot clearly conclude to a disturbance for disgust processing due to the weak percentage of errors in all conditions.

Some limitations should be considered in the interpretation of the present results. First, because of the low incidence of the insular epilepsy surgeries, we could only recruit a relatively small number of patients with such resections, which limited our capacity to detect hemispheric or

subregion (e.g., anterior vs. posterior insula) differences within this group. Most of resections in the insular group were operculo-insular or combined with temporal lobectomy rather than purely insular, and thus, the emotional interference impairments may be attributable to a set of structures rather than the insula uniquely. Another limitation relates to our Dot-Probe task: as the ISI and the probe presentation duration were not randomised, the effect of "inhibition of return" (IOR) (i.e., an effect whereby people are slower to respond to a target presented at a recently stimulated location as compared to a target presented at a new location) may explain the absence of attentional bias in our three groups [76]. Randomisation of ISIs and probe presentation durations, and the addition of a third stimulus presentation duration (e.g., 500 ms), might have helped reduce the IOR effect. This preliminary study indicates that the insular resection can lead a significant alteration in emotional interference control capacity, although more investigations with larger samples and more homogeneous procedures would be necessary to support this finding.

Conclusion

In conclusion, this study provides additional evidence supporting the inclusion of social and emotional processing assessments in neuropsychological test batteries aimed to detect functional impairments associated with insular cortex epilepsy and/or surgery. As mood and anxiety are frequent among patients with epilepsy and may interfere with quality of life even when seizure freedom is achieved after epilepsy surgery [77], the development of standardized neuropsychological tests to detect disturbance in affective information processing is needed as it may lead to better identification and prediction of psychological disorders in this population.

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CHAPITRE IV : DISCUSSION GÉNÉRALE

Discussion des articles

1. Rappel de la problématique et de l'objectif général

Sur la base des premières études de stimulation électro-corticale directe menées auprès de patients éveillés subissant une neurochirurgie, l'insula a longtemps été considérée essentiellement comme une partie du « cerveau viscéral » (78). Depuis lors, cependant, une accumulation de données a suggéré que cette structure est impliquée dans divers aspects neuropsychologiques plus complexes tels que dans les fonctions sensorielles, attentionnelles et affectives (8). Or, les découvertes scientifiques en recherche fondamentale et clinique ont parfois été contradictoires quant au rôle de l'insula dans le traitement des informations. De plus, la recherche dans ce domaine demeure limitée, notamment en raison de la rareté des lésions acquises circonscrites à l'insula, ainsi qu'imprécise, attribuable à la faible résolution spatiale ou temporelle intrinsèque aux techniques d'investigation usuelles (133, 209). Depuis l'avènement des techniques de microchirurgie, la résection insulaire partielle ou complète chez les patients atteints d'épilepsie insulaire pharmaco-résistante est de plus en plus fréquente, avec des résultats favorables quant au contrôle des crises (57, 206, 207). Or, les atteintes neuropsychologiques rattachées à une insulectomie demeurent mal connues. Il est donc important d'investiguer davantage ces répercussions sur le fonctionnement neuropsychologique. De plus, ces atteintes permettraient de mieux comprendre la contribution de l'insula au fonctionnement neuropsychologique. D'autre part, l'excellente résolution spatiale et temporelle de l'iEEG en fait un outil de prédilection dans l'étude fonctionnelle des structures profondes telles que l'insula (202). Ainsi, l'objectif principal de cette thèse est de préciser la nature de la contribution de l'insula au traitement de l'information sensorielle, saillante, attentionnelle et émotionnelle à l'aide de mesures neurophysiologiques menées en iEEG auprès de patients avec des électrodes implantées dans l'insula dans le cadre d'une évaluation préchirurgicale, ainsi qu'au moyen d'évaluations cliniques auprès de

patients ayant subi une insulectomie unilatérale partielle ou complète pour le traitement de crises épileptiques résistantes à la médication.

2. EEG intracrânien : articles I & II

2.1 Rappel du premier objectif et de l'hypothèse générale

Le premier objectif de cette thèse vise à documenter les contributions respectives de l'insula antérieure et de l'insula postérieure au traitement attentionnel pour les informations visuelles et auditives. Notre hypothèse de recherche était que l'insula antérieure répondrait à un stade tardif du traitement attentionnel, lors de la détection d'informations pertinentes auditives et visuelles telles que des stimuli caractérisés en tant que *cibles*, reflétant ainsi un traitement attentionnel volontaire de type *top-down*. L'insula postérieure, quant à elle, interviendrait à un stade précoce du traitement attentionnel, lors de la présentation d'informations saillantes auditives, pertinentes ou non à la tâche, telles que des stimuli *cibles*, *nouveaux* et *familiers*, traduisant un traitement attentionnel automatique de type *bottom-up*. Ce premier objectif a été investigué au moyen d'enregistrements en EEG intracrânienne lors de la passation de tâches de type *oddball* visuel et auditif (passif et actif). Afin de répondre à nos hypothèses, le tracé iEEG a été analysé en potentiel évoqué (c.-à-d. ERP N100, P3a et P3b) et en temps-fréquence (c.-à-d. bandes de fréquences thêta, alpha, gamma et haut gamma).

2.2 Synthèse des résultats

Notre première étude en EEG intracrânienne, menée auprès de 8 patients atteints d'épilepsie, a pour but d'examiner l'implication de l'insula dans le traitement attentionnel envers l'information visuelle à l'aide d'une tâche d'attention de type *oddball actif* en modalité visuelle. Des électrodes en profondeur implantées dans 10 lobes insulaires (5 gauches et 5 droits) pour un total de 59 contacts d'électrodes insulaires ont été enregistrées. **L'hypothèse spécifique** était que l'insula antérieure

répondrait exclusivement au stimulus pertinent à la tâche (c.-à-d. la cible), indexé par la présence d'oscillations tardives en fréquence haut gamma (70-150 Hz) et de la composante P3b enregistrées suivant la présentation du stimulus cible, traduisant ainsi un traitement attentionnel volontaire. Aucune activité oscillatoire en fréquence haut gamma, ni aucun indexage de la composante P3b n'était attendu dans l'insula postérieure suivant la présentation des trois stimuli visuels (c.-à-d. cible, nouveau et standard).

Les résultats de cette première étude ont montré que la présentation du stimulus cible était associée à l'indexage de la composante P3b (de 250 à 338 ms) pour 39 % des contacts d'électrodes implantés dans la portion antérieure de l'insula. Parmi ces contacts, l'amplitude était plus élevée pour le stimulus cible en comparaison aux stimuli standards (100 %) et nouveaux (72 %). Une augmentation de l'activité oscillatoire dans la bande de fréquence haut gamma (de 200 à 300 ms) en réponse au stimulus cible était également observée pour 53 % des contacts dans l'insula antérieure. Pour tous ces contacts, l'augmentation était plus élevée pour le stimulus cible comparativement aux stimuli standards et nouveaux. Au contraire, très peu de contacts localisés dans la portion postérieure de l'insula ont enregistré une déflexion P3b (16 %) en réponse à la détection de la cible. Par ailleurs, des oscillations tardives dans la bande de fréquence haut gamma (de 400 à 500 ms) ont été enregistrées sur 43 % des contacts de l'insula postérieure, suggérant davantage un traitement sensori-moteur (lié à la réponse motrice aux cibles) plutôt qu'attentionnel. Les résultats de ce premier article soulignent l'implication de l'insula antérieure dans le traitement attentionnel volontaire de type *top-down* pour la détection des informations visuelles pertinentes relatives à la tâche demandée. L'insula postérieure, quant à elle, ne semble pas impliquée dans le traitement attentionnel contrôlé.

Notre deuxième étude en EEG intracrânienne menée sur 8 patients atteints d'épilepsie a, quant à elle, pour but d'examiner la dynamique spatio-temporelle du traitement de l'information

auditive au sein de l'insula à l'aide de deux tâches attentionnelles de type *oddball passif* et *actif* en modalité auditive. Un total de 62 contacts d'électrodes insulaires a été enregistré à travers 11 lobes insulaires (6 gauches et 5 droits). **L'hypothèse spécifique** était que l'insula antérieure répondrait spécifiquement au stimulus pertinent (c.-à-d. la cible) lors de la tâche *active*, reflété par l'indexage de la composante P3b et par la présence d'activités oscillatoires tardives en fréquence thêta (4-7 Hz), alpha (8-12 Hz), gamma (30-50 Hz) et haut gamma (70-150 Hz) suivant la présentation du stimulus cible, traduisant ainsi un traitement attentionnel volontaire. Lors de la tâche *passive*, aucune réponse spécifique de l'insula antérieure n'était attendue, pour aucun type de stimulus (c.-à-d. cible, nouveau et standard). L'insula postérieure, quant à elle, répondrait précocement à tout type de stimuli auditifs, indépendamment de leur pertinence et de la nature de la tâche attentionnelle demandée (*active* ou *passive*), reflété par la présence d'activités oscillatoires précoces en fréquence thêta, alpha, gamma et haut gamma suivant la présentation de stimuli auditifs cibles, nouveaux et standards, ainsi que par l'indexage d'une déflexion N100, lesquels traduiraient un traitement attentionnel automatique.

Les résultats de cette deuxième étude ont montré que la majorité des contacts d'électrodes implantés dans l'insula postérieure présentait une déflexion N100 autour de 100 ms suivant la présentation des stimuli auditifs, indépendamment de la tâche (c.-à-d. *passive,* 83 % ou *active,* 79 %) et du type de stimulus, tandis que seulement 19 % des contacts d'électrodes localisés dans l'insula antérieure indexaient cette déflexion (*oddball actif* et *passif*). Les analyses en temps-fréquence sur l'intervalle de temps de 50-150 ms poststimulus pour la tâche *passive* ont montré une augmentation d'activités oscillatoires en fréquences thêta et alpha (c.-à-d. puissances fréquentielles augmentées pour le stimulus standard comparé aux stimuli déviants), ainsi qu'en fréquences gamma et haut gamma (c.-à-d. puissances fréquentielles augmentées pour le stimulus déviant aigu > standard > déviant grave) dans les contacts d'électrodes de l'insula postérieure en comparaison à ceux implantés

en antérieure. Ces résultats suggèrent que l'insula postérieure est impliquée dans le traitement automatique de l'information auditive. D'autre part, la présentation du stimulus cible était associée à l'indexage de la composante P3b (de 230 à 394 ms) pour 41 % des contacts d'électrodes implantés dans l'insula antérieure dans la tâche *active*, tandis qu'aucune déflexion P300 (P3a et P3b) n'a été observée au sein de l'insula antérieure et postérieure dans la tâche *passive*. Parmi ces contacts en antérieur, l'amplitude était plus élevée pour le stimulus cible en comparaison aux stimuli nouveaux (77 %) et standards (100 %). Les analyses en temps-fréquence sur l'intervalle de temps de 250-600 ms poststimulus pour la tâche *active* ont montré qu'une majorité des contacts d'électrodes implantés dans l'insula antérieure présentait une augmentation d'activités oscillatoires en fréquence thêta (91 %), alpha (67 %), gamma (56 %) et haut gamma (47 %) suivant la présentation du stimulus cible. Ces réponses oscillatoires étaient pour la majorité des contacts plus importantes pour le stimulus cible en comparaison aux stimuli standards (*M* = 96.5 %) et nouveaux (*M* = 46.8 %). Au contraire, peu de contacts localisés dans l'insula postérieure ont montré des modulations fréquentielles thêta (14 %), alpha (7 %), gamma (11 %) et haut gamma (23 %) liées à la présentation du stimulus cible dans cet intervalle de temps. Ces résultats soulignent la contribution de l'insula antérieure au traitement attentionnel volontaire pour l'information auditive.

2.3 Discussion des articles I et II

Intégration des résultats avec les données empiriques existantes

Les deux premières études de cette thèse fournissent un appui empirique en faveur de l'hypothèse selon laquelle les portions antérieure et postérieure de l'insula jouent des rôles distincts dans le traitement attentionnel pour l'information visuelle et auditive. L'ensemble des résultats obtenus en EEG intracrânienne souligne l'implication de l'insula antérieure dans le traitement attentionnel volontaire pour l'information visuelle et auditive, sous-tendue par un mécanisme

attentionnel dit *top-down* reflété par la genèse de la composante P3b en réponse à la détection des stimuli cibles visuels et auditifs, ainsi que par la présence d'activités oscillatoires tardives en fréquence thêta, alpha, gamma et haut gamma suivant leur détection, corroborant ainsi les données existantes en neuroimagerie (46, 176, 181, 210, 211) et en EEG de surface (135, 147). De plus, appuyée par les études de stimulation électro-corticale du cortex insulaire, lesquelles suggèrent une implication de l'insula postérieure dans le traitement de l'information sensorielle (5, 56, 57), notre deuxième étude met en exergue le rôle de l'insula postérieure dans le traitement attentionnel automatique pour l'information sensorielle, sous-tendu par un mécanisme attentionnel dit *bottom-up* indexé par la déflexion N100 suivant la présentation de stimuli auditifs, indépendamment de la nature de la tâche et de la pertinence des stimuli, ainsi que par la présence d'activités oscillatoires précoces en fréquence thêta, alpha, gamma et haut gamma suivant l'apparition des stimuli auditifs.

La mise en commun de l'ensemble des résultats obtenus dans ces deux études appuie également les travaux empiriques ayant rapporté des connexions variées de l'insula avec les autres structures cérébrales du cerveau (27-29). Plus spécifiquement, l'insula est connectée avec plusieurs régions frontale, temporale et pariétale sollicitées lors de tâches d'attention sélective visuelle et auditive, notamment le cortex orbito-frontal, le gyrus frontal inférieur, moyen et supérieur, le gyrus précentral, les opercules frontal et pariétal et le gyrus temporal supérieur, moyen et inférieur, ainsi que le cortex occipital latéral, le cortex cingulaire et le thalamus (53, 147, 212). Bien qu'il y ait certaines connexions partagées entre les portions insulaires antérieure et postérieure avec ces structures, l'insula antérieure s'avère principalement connectée avec les régions frontales, lesquelles sont impliquées dans des tâches requérant un contrôle attentionnel volontaire (8, 212, 213). L'insula postérieure, quant à elle, serait davantage connectée avec les aires somato-sensorielles, notamment les aires auditives primaires et associatives, ainsi que le sulcus temporal supérieur, compatible avec

un rôle dans le traitement attentionnel précoce de bas niveau envers l'information auditive afférente (8, 214, 215). Ainsi, les implications disparates entre les portions antérieure et postérieure de l'insula dans le traitement attentionnel observées lors de nos tâches *oddball* visuel et auditif seraient en accord avec leurs connexions respectives.

Différences inter-individuelles dans le traitement de l'information

Nos résultats en potentiels évoqués et en modulations fréquentielles obtenus à travers ces deux recherches démontrent une dissociation franche entre les portions antérieure et postérieure de l'insula dans le traitement attentionnel pour l'information visuelle et auditive. Cependant, il est pertinent de relever certaines variabilités inter-interindividuelles dans le processus attentionnel observées au sein de l'insula, indexées notamment par la présence de la composante P3b mesurée sur des contacts d'électrodes localisés dans la portion postérieure (c.-à-d. *oddball* visuel : 16 % ; *oddball* auditif : 39 %) et l'absence de cette dernière chez certains patients avec des contacts d'électrodes situés dans la portion antérieure (c.-à-d. *oddball* visuel : deux patients ; *oddball* auditif : un patient), ainsi que par l'indexage de la déflexion N100 enregistrée sur des contacts dans l'insula antérieure (c.-à-d. *oddball* auditif passif et actif : Pt. # 4, 19 % des contacts en antérieur). D'autre part, certains contacts d'électrodes localisés dans l'insula antérieure ont généré des oscillations précoces en fréquence alpha (6 %) et thêta (16 %), alors que d'autres implantés dans la portion postérieure ont produit des oscillations tardives en fréquence haut gamma (23 %), gamma (11 %), alpha (7 %) et thêta (14 %) suivant la détection du stimulus cible auditif. Ces variabilités dans le traitement de l'information au sein de l'insula peuvent s'expliquer tout d'abord par l'épilepsie, une condition neurologique qui peut induire une réorganisation anatomo-fonctionnelle (216-218). De plus, la présence de dysplasies corticales frontales et insulaires chez certains de nos patients peut également être associée à des restructurations corticales et sous-corticales (219, 220). Enfin, les connectivités

fonctionnelles réciproques intra-insulaires plaident en faveur de l'hypothèse que l'information sensorielle pourrait être véhiculée entre les différents gyri insulaires de l'insula antérieure et postérieure à plusieurs stades temporels du traitement de l'information (30).

Latéralité et division dorso-ventrale de l'insula antérieure

Nos données ne supportent pas l'hypothèse d'une prédominance hémisphérique dans le traitement attentionnel involontaire et volontaire envers des informations visuelles et auditives au sein de l'insula. Certains auteurs ont proposé une prédominance de l'hémisphère droit lors de tâches attentionnelles requérant la détection de stimuli cibles (147, 178), tandis que d'autres proposent une activation prépondérante de l'insula gauche (177, 181) ou bilatérale (53). Toutefois, les indexages des déflexions N100 et P3b, ainsi que les oscillations fréquentielles thêta, alpha, gamma et haut gamma mesurés à travers les tâches d'*oddball* visuel et auditif ne différaient pas en termes de latence, d'amplitude, de durée, ainsi que d'occurrence entre les deux hémisphères. La portion antérieure de l'insula est une région cérébrale impliquée dans le traitement de la saillance des stimuli, d'une part à travers le « réseau de saillance » dans lequel sa partie dorsale antérieure droite jouerait un rôle crucial de *monitor* influençant les activations des deux larges réseaux neuronaux (c.-à-d. réseau central exécutif et réseau du mode par défaut) (173) et d'autre part, par sa connexion unilatérale droite avec le « réseau attentionnel fronto-pariétal ventral » (221-226). La partie ventrale de l'insula antérieure est, quant à elle, engagée durant des tâches affectives et émotionnelles et connectée notamment avec les aires limbiques (8, 227). Une étude récente portant sur la myéline insulaire *in vivo* en IRM a mis en évidence une divergence myélo-architectonique entre les parties ventrale et dorsale de l'insula antérieure affiliée à des fonctions distinctes, dont la partie ventrale se rattache aux fonctions émotionnelles et affectives, tandis que la partie dorsale s'affilie aux processus inhibiteurs, au contrôle cognitif et à la mémoire de travail (228). Ainsi, l'identification et la manipulation des informations

saillantes impliqueraient le recrutement de l'insula antérieure droite dorsale spécifiquement, laquelle est recrutée dans le traitement attentionnel à travers son implication dans le réseau attentionnel et de saillance. Cette assertion nuance alors notre conclusion quant à l'absence d'une prédominance de l'insula antérieure droite par le fait de ne pas avoir considéré une sous-division ventro-dorsale de l'insula antérieure dans nos analyses.

Traitement de la pertinence extrinsèque du stimulus par l'insula

Bien que certaines études en neuroimagerie aient rapporté une activation de l'insula antérieure en réponse à la présentation de stimuli nouveaux (53, 178), nos résultats n'ont pas mis en évidence un indexage de la composante P3a dans l'insula antérieure suivant la présentation des stimuli nouveaux non pertinents à la tâche, en modalité auditive ou visuelle, lequel soulignerait un traitement pré-attentionnel de type *bottom-up* envers l'information saillante (c.-à-d. intrinsèquement pertinente). Contrairement à une étude récente de Blenkmann et de ses collaborateurs (229) menée en EEG intracrânienne, laquelle a documenté l'implication de l'insula dans la détection automatique de stimuli auditifs déviants, reflétée par la présence d'une déflexion *Mismatch Negativity* (MMN) vers 140-220 ms suivant la présentation de stimuli déviants, des analyses complémentaires sur la tâche d'*oddball* auditif passive n'ont pas mis en exergue la présence de la MMN (voir Annexe Tableau 1), laquelle surviendrait 50 ms après l'indexage de la N100 et traduirait un traitement pré-attentionnel faisant appel à la mémoire sensorielle (136, 146). Ainsi, nos résultats suggèrent plutôt que l'insula antérieure réponde à la pertinence extrinsèque du stimulus (c.-à-d. la pertinence reflétée par la tâche demandée) plutôt qu'à sa saillance intrinsèque ou à sa rareté (46, 112, 122, 202, 214, 230). Toutefois, considérant le rôle majeur de l'insula antérieure dans le traitement des stimuli émotionnels, ainsi que sa place cruciale dans le réseau de saillance, où l'initiation attentionnelle envers les stimuli saillants est opérée par l'insula antérieure (231), il ne peut être *a priori* réfuté que l'insula antérieure ne soit

pas impliquée dans la détection de stimuli saillants nouveaux intrinsèquement émotionnels. D'ailleurs, une étude menée en MEG a rapporté une activation précoce de l'insula antérieure, indexée par une déflexion MMN, en réponse à la saillance prosodique de stimuli affectifs vocaux (211).

Comparaison du décours temporel pour le traitement des stimuli auditifs et visuels

Notre composante P3b mesurée durant les tâches d'*oddball* et apparaissant lors de la détection des stimuli cibles visuels et auditifs est générée par l'insula antérieure de manière semblable pour les deux modalités en matière de latence (visuel : *M* = 288 ms ; auditif : *M* = 329 ms) et d'amplitude (visuel : *M* = 36 µV ; auditif : *M* = 24 µV). Bien que certaines études menées en EEG de surface aient rapporté une réponse P3b plus précoce lors de la présentation de stimuli auditifs cibles comparativement aux cibles visuelles, sous-jacent à la distribution de sites générateurs distinguables entre ces deux modalités (232-234), nos deux recherches suggèrent que l'insula antérieure répond aux stimuli cibles visuels et auditifs dans un décours temporel similaire qui traduit un traitement attentionnel volontaire aux alentours de 300 ms poststimulus indépendamment de la modalité sensorielle. De plus, des analyses complémentaires en potentiel évoqué menées sur la tâche d'*oddball* visuel dans l'intervalle de temps de la déflexion visuelle P100, laquelle est comparable à la déflexion auditive N100 et traduisant un traitement attentionnel précoce pour l'information visuelle, n'ont montré aucune déflexion P100 mesurée dans l'insula suivant la présentation des stimuli visuels (voir Annexe Tableau 2), suggérant que l'implication de l'insula dans le traitement attentionnel pour l'information visuelle se traduit par le déploiement de ressources attentionnelles volontaires pour les informations visuelles pertinentes plutôt qu'un traitement sensoriel précoce de bas niveau.

Les modulations oscillatoires en fréquences haut gamma et thêta observées suivant la détection des cibles visuelles et auditives sur nos tâches d'*oddball* visuel et auditif actif plaident également en faveur d'un décours temporel similaire dans le traitement des stimuli cibles entre les

deux modalités. Des analyses complémentaires effectuées sur le tracé iEEG de notre tâche visuelle ont mis en évidence une modulation thêta pour 44 % des contacts d'électrodes localisés dans l'insula antérieure suivant la détection du stimulus cible visuel dans un intervalle moyen de 200-400 ms poststimulus (*M* = 308 ms) (voir Annexes Tableau 3 et Figure 1), proposant ainsi une modulation thêta temporellement similaire à celle observée dans la tâche auditive (*M* = 328 ms). Concernant la bande de fréquence haut gamma, la modalité visuelle présente un intervalle de temps moyen légèrement plus long rattaché à la détection de la cible visuelle (de 200 à 650 ms ; *M* = 475 ms) que celui pour la cible auditive (de 200 à 450 ms ; *M* = 347 ms). Ainsi, ces intervalles de temps d'oscillations haut gamma et thêta concordent avec plusieurs travaux menés en EEG de surface et intracrânienne rapportant la présence d'oscillations haut gamma et thêta dans ces intervalles de temps lors de tâches d'attention sélective (157, 159, 160, 162-166). De plus, Canolty et ses collaborateurs (167) ont proposé que la fréquence haut gamma soit verrouillée en phase avec les oscillations thêta. En résumé, l'ensemble des données obtenues convergent sur un intervalle de temps similaire dans le traitement attentionnel volontaire entre ces deux modalités opéré par l'insula antérieure.

Phénomène attentionnel et interprétation alternative

Bien que nos conclusions s'appuient sur une approche dichotomique de l'attention (c.-à-d. processus bottom-up et top-down) pour mettre en exergue l'implication des portions antérieure et postérieure de l'insula dans le traitement de l'information, plusieurs auteurs ont proposé que le phénomène « attentionnel » regroupe plutôt un ensemble de mécanismes de sélection/d'action au sein d'un système de traitement parallèle, dynamique et continu dans lequel les processus sensori-cognitivo-moteurs interagiraient, contestant ainsi les divisions binaires des processus attentionnels (235-238). Dans cet ordre d'idées, nos résultats, interprétés comme supportant le rôle de l'insula

antérieure dans le traitement attentionnel volontaire pour l'information visuelle et auditive pourraient ainsi également être interprétés comme supportant une implication de cette structure dans la préparation de la réponse suivant la détection de la cible. À l'aide d'une tâche de *oddball* émotionnel, Campanella et ses collaborateurs (239) ont tenté de dissocier au moyen des composantes N2b/P3a et P3b les processus liés au changement de l'attention (c.-à-d. l'orientation attentionnelle) de ceux de la réponse comportementale (c.-à-d. la préparation de la réponse). Leurs résultats ont montré une composante N2b dans la région occipitale aux alentours de 230 ms suivant la présentation d'images émotionnelles, alors qu'une composante P3b dans la région pariétale a été obtenue aux alentours de 450 ms suivant la présentation de stimuli émotionnels cibles (à détecter), laquelle reflèterait la préparation à la réponse prémotrice. En s'appuyant sur cette étude, nos résultats ne suggèrent pas une implication de l'insula antérieure dans la déviation du foyer attentionnel, laquelle se manifesterait par la présence de la composante P3a à la suite de la présentation des stimuli nouveaux et cibles, mais cela n'exclut pas *a priori* que la présence de notre P3b ne reflèterait pas la préparation d'une réponse comportementale. Par ailleurs, au moyen de tâches *oddball* visuel et auditif menées en IRMf-EEG combiné, Linden et ses collaborateurs (180) ont associé la détection des stimuli cibles à une activation bilatérale de l'insula aux alentours de la latence de la composante P3b, indépendamment de la modalité et de la condition de réponse, laquelle était soit motrice (c.-à-d. presser sur une touche), soit mentale (c.-à-d. comptage silencieux des cibles), infirmant ainsi la contribution exclusive de l'insula à la préparation d'une réponse motrice. En ce qui concerne nos études en iEEG, un prétest effectué sur la tâche *oddball* visuel auprès de deux patientes (Pt. # 5 et # 6) incluait deux versions de la tâche *oddball* distinguables selon la réponse à la cible demandée (c.-à-d. motrice ou mentale). Les résultats obtenus avec ces deux versions concernant l'émergence de la composante P3b dans l'insula antérieure se sont avérés spatio-temporellement similaires, suggérant

que la genèse de la P3b dans l'insula antérieure ne serait pas nécessairement liée à la préparation de la réponse motrice. Toutefois, il est important de considérer que ces dernières données reposent sur un échantillon très faible de contacts d'électrodes, d'autant que plusieurs études ont documenté une activation de l'insula lors de la sélection des actions dans une tâche de prise de décision (240), ainsi que lors de la préparation à l'inhibition d'une réponse comportementale dans une tâche de stop-signal (241). De ces faits, d'autres études seront nécessaires afin de mieux positionner la contribution de l'insula antérieure au traitement de l'information.

3. Évaluations cliniques : articles III & IV

3.1 Rappel du deuxième objectif et de l'hypothèse générale

Le second objectif de cette thèse vise à mieux comprendre les conséquences neuropsychologiques d'une insulectomie sur le traitement sensoriel et affectivo-attentionnel. Notre hypothèse de recherche était qu'une résection insulaire entraînerait des altérations dans le traitement de l'information multisensorielle reflétées par des perturbations sensorielles dans le seuil de sensibilité, dans l'évitement des sensations, ainsi que dans l'enregistrement et la recherche sensorielle. De plus, des difficultés dans le traitement attentionnel et dans les capacités d'inhibition envers les informations aux contenus émotionnels étaient également attendues. Pour répondre à ces conjectures, des évaluations comportementales ont été menées auprès de patients ayant subi une résection unilatérale partielle ou complète de l'insula pour une épilepsie réfractaire à la médication. Une première étude a investigué le traitement de l'information multisensorielle à l'aide du questionnaire du profil sensoriel de Dunn (AASP) (208) tandis qu'une seconde étude a évalué le traitement affectivo-attentionnel et les capacités d'inhibition pour l'information affective au moyen d'une tâche Dot-Probe émotionnelle et d'un test de Stroop émotionnel. Pour chaque étude, les

réponses et les performances ont été comparées à un groupe de « lésion-contrôle » constitué de patients ayant subi une lobectomie temporale, incluant une amygdalo-hippocampectomie sélective, pour le contrôle d'une épilepsie réfractaire à la médication, ainsi qu'à un groupe de participants sains.

3.2 Synthèse des résultats

Notre troisième étude menée au moyen du questionnaire d'autoévaluation du profil sensoriel de Dunn auprès de 17 patients ayant subi une chirurgie d'épilepsie insulaire a pour objectif d'examiner les changements dans le profil sensoriel suivant une résection insulaire unilatérale. **L'hypothèse spécifique** était qu'une résection insulaire serait associée à des altérations globales dans le traitement multisensoriel. Plus spécifiquement, des difficultés sensorielles de sévérités légères à modérées étaient attendues en ce qui a trait aux modalités sensorielles olfacto-gustatives, tactiles, auditives et viscérales, ainsi qu'une sensibilité sensorielle augmentée. Ces perturbations se présenteraient par des scores « inférieurs » sur les quadrants comportementaux du questionnaire de Dunn mesurant l'évitement, l'enregistrement et la recherche sensorielle comparativement aux patients ayant subi une chirurgie d'épilepsie temporale et aux participants sains.

Les résultats de cette troisième étude ont montré que les résections insulaires étaient associées à des altérations relativement légères du traitement de l'information sensorielle. Plus spécifiquement, les résections insulaires et temporales chez les patients atteints d'épilepsie réfractaire à la médication étaient associées à une recherche de sensation sensorielle moindre, reflétant un manque d'exploration pour les informations sensorielles dans l'environnement. De plus, les réponses comportementales dites actives étaient particulièrement altérées dans la modalité sensorielle olfacto-gustative pour les patients ayant subi une résection insulaire.

Notre quatrième étude menée au moyen d'une évaluation neurocomportementale auprès de 16 patients ayant subi une chirurgie d'épilepsie insulaire a pour objectif d'examiner la capacité du contrôle des interférences et les biais attentionnels pour l'information émotionnelle suivant une résection unilatérale partielle ou complète de l'insula, à l'aide d'une tâche Dot-Probe émotionnelle incluant des images de peur et de dégoût, ainsi que d'un test de Stroop émotionnel contenant des mots intrinsèquement négatifs. **L'hypothèse spécifique** était qu'une résection insulaire serait associée à des altérations globales dans la capacité à traiter l'information affective (c.-à-d. mots et images émotionnels). Pour la tâche Dot-Probe émotionnelle, des difficultés dans l'engagement ou le désengagement attentionnel étaient attendues, en particulier pour le traitement des images à connotation de dégoût chez les patients ayant subi une insulectomie, alors que la chirurgie du lobe temporal serait spécifiquement associée à des facultés affaiblies dans le traitement des images de peur. Ces perturbations se traduiraient par des temps de réaction (ms) plus lents pour traiter ces images affectives comparativement à la performance des participants sains. De plus, les symptomatologies dépressives et anxiogènes seraient positivement corrélées à la présence de biais attentionnels et aux capacités de contrôle des interférences émotionnelles. Pour le test de Stroop émotionnel, un temps de complétion (ms) plus long pour nommer les couleurs des mots émotionnels comparativement aux mots neutres (c.-à-d. Stroop classique) était attendu chez les patients ayant subi une insulectomie, alors que cette différence de temps de réponse entre les deux conditions du test de Stroop n'était pas attendue auprès des patients ayant subi une chirurgie d'épilepsie temporale, ni auprès des participants sains.

Les résultats de cette quatrième étude ont montré que la résection insulaire unilatérale partielle ou complète était associée à une légère perturbation du contrôle des interférences pour l'information affective, reflétée par un temps de complétion plus long pour nommer la couleur des

mots émotionnels du test de Stroop émotionnel par rapport aux mots neutres. En revanche, aucun effet néfaste des chirurgies d'épilepsie insulaire et temporale n'a été trouvé dans le traitement affectivo-attentionnel comme en témoigne les performances de nos deux groupes cliniques dans la tâche Dot-Probe émotionnelle pour laquelle aucun biais attentionnel n'a été mis en évidence. De plus, les symptomatologies dépressives et anxiogènes n'étaient pas corrélées avec les performances attentionnelles et les capacités d'inhibition.

3.3 Discussion des articles III et IV

Intégration des résultats de l'article III avec les données empiriques existantes

Les découvertes reliées à l'étude par questionnaire mettent en exergue la présence d'altérations sensorielles relativement légères à modérées associées aux résections unilatérales d'épilepsie insulaire, notamment dans le pattern comportemental se référant à la recherche sensorielle, lequel traduit un manque d'exploration et d'engagement envers les stimuli environnementaux. Les réponses comportementales dites actives envers les stimuli olfacto-gustatifs semblent être particulièrement altérées à la suite d'une ablation insulaire. Ces découvertes concordent avec les études de stimulation électro-corticale ayant documenté des réponses gustatives suivant la stimulation de l'insula (38, 42, 56-58, 72), ainsi qu'avec les études de lésion ayant rapporté des perturbations olfacto-gustatives suivant un dommage insulaire (34, 63, 68). En somme, l'ensemble des résultats rapportés dans cette troisième étude plaide en faveur d'une caractérisation de l'insula comme le « site de convergence multimodal » où seraient acheminées les informations des divers systèmes sensoriels et dont une lésion peut conduire à des manifestations de déficits sensoriels variables.

Altérations sensorielles et modalités

La représentation du goût nécessite la combinaison des inputs sensoriels olfactifs et gustatifs, ainsi que ceux des sensations viscérales, lesquels sont véhiculés au sein de l'insula suivant une intégration caudo-rostrale de l'information (31, 69). En effet, considérant que la portion dorso-postérieure de l'insula est impliquée dans le traitement des sensations viscérales et que les inputs olfacto-gustatifs convergent dans le cortex gustatif primaire, lequel est localisé dans le cortex insulaire (71, 242-246), il n'est pas surprenant qu'une résection insulaire soit associée à des altérations du traitement olfacto-gustatif. Comme le suggère les données de notre troisième étude, une résection insulaire serait associée à une hypersensibilité aux stimuli olfacto-gustatifs, laquelle se traduit par un besoin réduit d'apport sensoriel intense dans cette modalité. Cette observation est compatible avec des études cliniques ayant rapporté des difficultés dans l'estimation de l'intensité perçue pour les stimuli olfacto-gustatifs suivant un dommage insulaire (34, 63), ainsi qu'avec l'étude de Boucher et de ses collaborateurs (33), laquelle a rapporté des cas d'hyperacousie suite à une lésion insulaire unilatérale. De plus, bien que des études en neuroimagerie et une étude de lésion ont suggéré que l'insula serait une région clé dans le système vestibulaire et dans la perception du *self-motion* (73-75), nos données n'appuient pas la présence de perturbations dans le traitement vestibulaire à la suite d'une résection insulaire. En outre, il est quelque peu surprenant que nos résultats n'aient pas démontré d'altérations dans le comportement auditif compte tenu du large éventail de preuves cliniques associant les dommages insulaires à des plaintes dans le traitement de l'information auditive (48-51). La modalité visuelle semble, elle aussi, plutôt bien préservée suivant une résection insulaire. Toutefois, il se pourrait que les items du questionnaire rattachés à ces modalités n'aient pas été suffisamment sensibles pour faire ressortir certaines perturbations comportementales auditives et visuelles telles que des hallucinations, des agnosies et/ou des difficultés dans la reconnaissance des

stimuli. Le questionnaire de Dunn mesure des patterns comportementaux sensoriels spécifiques dont l'enregistrement, la recherche, la sensibilité et l'évitement des sensations sensorielles ; il se pourrait ainsi que d'autres perturbations sensorielles se manifestent suivant une résection insulaire, notamment en ce qui a trait à la capacité de discrimination sensorielle, la mémoire sensorielle ou encore le contrôle des distractions sensorielles.

Intégration des résultats de l'article IV avec les données empiriques existantes

La mise en évidence d'une perturbation du contrôle des inférences émotionnelles chez les patients ayant subi une chirurgie d'épilepsie insulaire corrobore, d'une part, les travaux empiriques ayant singularisé l'insula antérieure en tant qu'un substrat neuronal crucial dans le réseau de saillance par son rôle dans la détection des informations ascendantes saillantes, telles que celles à connotation affective (173, 174, 226) et d'autre part, les études ayant proposé une implication de l'insula dans les processus d'inhibition (125, 132, 247), la conscience des erreurs (184) et dans la résolution des interférences (185, 186). Toutefois, nos données suggèrent que cette altération du contrôle des interférences serait influencée par le contenu affectif des distracteurs plutôt que par la difficulté de la tâche. En effet, les patients ayant subi une chirurgie d'épilepsie insulaire ont présenté des performances comparables aux patients avec une chirurgie d'épilepsie temporale et aux participants sains dans la condition du test de Stroop dit classique, appuyant ainsi l'étude de Boucher et de ses collaborateurs (64) laquelle n'a pas documenté de différence de performance entre les évaluations pré- et post-chirurgies d'épilepsie insulaire dans cette condition du test de Stroop. En outre, considérant le large éventail d'études en neuroimagerie ayant documenté une activation de l'insula lors de la présentation de stimuli affectifs (94, 111, 112), ainsi que les études de lésion rapportant des altérations dans la reconnaissance des émotions (119, 121), il est surprenant qu'aucun biais attentionnel n'ait été démontré envers les images à connotation de peur et de dégoût dans la

tâche Dot-Probe émotionnelle, d'autant que les deux premières études de cette thèse supposent un rôle de l'insula antérieure dans la détection des stimuli pertinents.

Appraisal émotionnel et insula

Bien que plusieurs études aient rapporté un rôle spécifique de l'insula dans le traitement de l'émotion du dégoût (113, 115-117, 248), les résultats de notre tâche Dot-Probe émotionnelle ne démontrent pas d'altérations spécifiques pour cette émotion, comme l'ont également suggéré certaines études de lésion (118-121). En outre, des travaux ont rapporté que l'implication de l'insula dans le traitement des évaluations des émotions serait influencée par le degré d'excitabilité lié au contenu émotionnel plutôt que par la valence ou par une émotion en particulier (111, 123) et que la reconnaissance du niveau d'*arousal* d'un stimulus émotionnel requérait la conscience intéroceptive (36, 45). Une étude en neuroimagerie a d'ailleurs documenté cette interaction entre la sensibilité aux indices intéroceptifs, l'expérience émotionnelle négative vécue et l'activité de l'insula antérieure (96). Le rôle de l'insula dans l'*appraisal* émotionnel se ferait donc par son implication dans l'intégration des signaux du milieu viscéral vers une représentation intéroceptive des états du corps sous-tendue par le niveau d'*arousal* émotionnel perçu. Il est donc plausible que l'excitabilité émotionnelle de nos images de peur et de dégoût n'avait pas un niveau suffisamment élevé pour déclencher ce processus chez nos participants sains, ceci pouvant ainsi expliquer l'absence de différence avec les groupes de patients ayant subi une chirurgie d'épilepsie insulaire et temporal. En se basant sur la recherche de Critchley et de ses collaborateurs (96) et des données comportementales de notre troisième étude, laquelle pourrait suggérer une altération des sensations viscérales à la suite d'une résection insulaire à large étendue spécifiquement (c.à.d. à plus de 65 % de la structure insulaire totale), il n'est pas exclu également que notre échantillon de patients ayant subi une chirurgie d'épilepsie insulaire, à majorité

d'envergure partielle, n'ait pas influencé « positivement » les performances recensées dans la tâche Dot-Probe.

4. Limites méthodologiques des études

L'ensemble des résultats de cette thèse devrait être interprété en prenant en considération certaines limites. En ce qui a trait aux deux premières études, leurs limitations incluent des facteurs inhérents à l'investigation en EEG intracrânienne avec des patients atteints d'épilepsie, notamment la couverture incomplète du cortex insulaire par les électrodes, ainsi que la restriction de la généralisation des résultats en raison de l'influence possible de la condition épileptique et des dysplasies corticales sur la réorganisation fonctionnelle de l'insula. En ce qui concerne les deux études en évaluation comportementales post-chirurgie d'épilepsie insulaire, la rareté de ce type de chirurgie d'épilepsie a mené au recrutement d'un nombre relativement modeste de patients avec une résection insulaire, limitant les possibilités de détecter des différences en fonction de l'hémisphère réséqué et/ou de la portion précise de l'insula impliquée dans la chirurgie. Un plus grand échantillon aurait pu fournir de précieuses informations sur les sous-divisions fonctionnelles au sein de l'insula. De plus, la plupart des résections insulaires étaient en réalité operculaire-insulaire ou combinées avec une lobectomie temporale plutôt que purement insulaire. Ainsi, nous ne pouvons exclure un rôle des opercules et des régions temporales au sein des déficits observés. De plus, une limitation inhérente à ce type d'études de lésion concerne la possibilité de mécanismes cérébraux compensatoires. Comme les résections insulaires de nos patients étaient unilatérales, nous ne pouvons pas écarter l'hypothèse que l'insula de l'hémisphère préservée pouvait, en partie, atténuer ou compenser les déficits fonctionnels constatés dans les capacités d'inhibition envers l'information émotionnelle et dans les altérations multisensorielles. Tel qu'amorcé par les données comportementales de notre troisième étude, la sévérité des déficits pourrait augmenter avec l'étendue de la résection insulaire, laissant

supposer qu'une lésion bilatérale du cortex insulaire aurait résulté en des altérations des processus attentionnels, émotionnels ou sensoriels plus marquées. Par ailleurs, il est important de relever que les patients implantés en vue d'une chirurgie d'épilepsie (articles I et II) ainsi que ceux recrutés en évaluations comportementales (articles III et IV) étaient pour la vaste majorité sous médication, une condition ayant des répercussions sur l'activité neuronale, ainsi que sur le plan cognitivo-affectif et comportemental de l'individu.

En ce qui a trait aux protocoles expérimentaux, la tâche Dot-Probe émotionnelle a été construite avec des temps de présentation non randomisés concernant l'intervalle interstimulus et l'indice. Considérant que les individus ont une diminution de la tendance à répondre à une cible présentée dans un endroit déjà récemment stimulé en comparaison à un nouvel emplacement (c.-à-d. effet de l'inhibition retour), des durées de présentation randomisées pourraient aider à réduire cet effet. De plus, les images émotionnelles pourraient être d'un niveau plus élevé d'excitabilité émotionnelle. Par ailleurs, notre questionnaire mesurant les changements sensoriels post-chirurgie pourrait ne pas avoir été suffisamment sensible pour détecter des altérations sensorielles subtiles chez les patients moins démonstratifs de leurs symptômes. De plus, il s'agit d'un questionnaire auto-déclaré en rétrospectif. Des évaluations sensorielles pré et postopératoires pourraient permettre de mieux objectiver les changements associés à la résection insulaire, de surcroît certaines altérations pourraient être présentes avant la chirurgie.

Une dernière limite porte sur l'interprétation de nos deux premières études concernant l'implication de l'insula antérieure dans le traitement de l'information. En effet, il apparaît plausible que l'activation de cette région insulaire suivant la présentation des stimuli cibles visuels et auditifs reflète la préparation d'une réponse plutôt qu'un traitement attentionnel. La suppression d'une réponse explicite suivant la détection du stimulus cible pourrait permettre de mieux définir

l'implication de l'insula dans le traitement de l'information. De plus, des analyses menées individuellement sur un ensemble de régions cibles impliquées dans des processus décisionnels, de planifications et d'exécutions (p.ex. régions motrices), ainsi que leurs connectivités réciproques pourraient permettre de mieux spécifier la place de l'insula dans le traitement de l'information lors d'une tâche *oddball*.

5. Implication clinique & recherches futures

Les résultats de la présente thèse fournissent un appui quant à la pertinence de développer des tests neuropsychologiques standardisés afin de mieux identifier et prédire les perturbations fonctionnelles associées à une épilepsie ou à une chirurgie du cortex insulaire. Au sein de la pratique clinique actuelle, les altérations sensorielles sont rarement évaluées de manière formelle dans le contexte d'une épilepsie ou d'une chirurgie insulaire. Pourtant, ces perturbations peuvent affecter les fonctions cognitives, sociales et affectives, ainsi que les performances fonctionnelles dans la vie quotidienne (249). Comme l'ont démontré nos données obtenues en EEG intracrânien et en évaluation par questionnaire, l'insula contribue au traitement de l'information auditive et visuelle et sa résection est associée à des perturbations dans le traitement sensoriel. D'autre part, l'évaluation neuropsychologique pré- et post-chirurgie d'épilepsie insulaire inclut principalement des outils psychométriques examinant les fonctions exécutives dites « froides » (p.ex. mémoire de travail, flexibilité cognitive, inhibition). Or, ces habilités cognitives sont plus rarement mesurées dans un contexte de nature affective. Pourtant, notre quatrième étude met en exergue que la résection insulaire est associée à une légère perturbation du contrôle des interférences pour l'information affective, suggérant une implication de cette structure dans le processus d'inhibition émotionnelle. Considérant qu'une faible capacité de contrôle d'inhibition émotionnelle est un facteur de vulnérabilité pour l'apparition, le maintien et la rechute de troubles psychiatriques dont les troubles

de l'humeur et l'anxiété (250-254), lesquels seraient d'ailleurs particulièrement prévalant chez les individus atteints d'épilepsie (255-257), la conception de nouveaux outils d'évaluation sensibles à ces types d'atteintes cognitivo-affectives s'avère nécessaire. Des tests neuropsychologiques standardisés permettraient de mieux anticiper et cerner les séquelles sensorielles et affectivo-cognitives sous-jacentes à l'épilepsie et à la chirurgie d'épilepsie insulaire afin de permettre la mise en œuvre d'interventions cliniques appropriées aux déficits. Ces tests psychométriques pourraient également servir d'appui à la localisation du foyer épileptogène selon les dysfonctions cérébrales mises en évidence. Afin de mieux caractériser les déficits expliqués par l'épilepsie ou par la chirurgie d'épilepsie insulaire et leur relation avec la localisation spécifique de la résection, une recherche future pourrait amener aux développements de tâches affectivo-cognitives standardisées par l'intermédiaire d'évaluations en phase pré- et post-chirurgie d'épilepsie insulaire afin de mesurer l'effet néfaste de l'épilepsie et/ou de la chirurgie du cortex insulaire sur la performance.

Dans la perspective de recherches futures, il serait intéressant d'investiguer en EEG intracrânienne la réponse de l'insula antérieure et postérieure suivant la présentation de stimuli intrinsèquement saillants, tels que des images et des sons émotionnels, au moyen de tâches attentionnelles actives et passives, de difficultés variables, tout en considérant également les réponses du système nerveux autonome rattachées au traitement de l'information (p.ex. variabilité de la fréquence cardiaque et mesure électrodermale). Ce projet permettrait ainsi d'objectiver le rôle de l'insula dans le traitement attentionnel *bottom-up* et *top-down* pour l'information affective et sa relation avec les états physiologiques du corps. De plus, des analyses de connectivité permettraient de rendre compte de la place spécifique de l'insula dans la dynamique spatio-temporelle du traitement de l'information affective. Par ailleurs, l'insula serait un substrat neuronal critique dans les comportements addictifs, notamment due à son implication dans l'intégration des états

physiologiques, dans le processus décisionnel et dans le contrôle cognitif tel que l'inhibition de stimuli saillants liés à la dépendance (258-262), ainsi que par son rôle crucial dans le réseau de saillance (263-265). Quelques études de lésion ont d'ailleurs proposé qu'un dommage insulaire perturberait l'état pathologique addictif préexistant (266, 267). D'autre part, le niveau d'activation de l'insula durant des tâches d'inhibition serait associé au maintien de l'abstinence du comportement addictif (259). La manifestation d'altérations attentionnelles précoces et/ou tardives et la présence d'interférence pour les informations saillantes reliées à l'état de dépendance pourrait ainsi refléter un dysfonctionnement de l'activité insulaire. Comme la stimulation magnétique transcrânienne peut provoquer une neuro-adaptation durable, la neuromodulation par stimulation de régions cérébrales spécifiques telles que l'insula ouvre la voie à de nouveaux traitements pour les pathologies telles que les addictions. Dans le même ordre d'idée, l'insula est de plus en plus pointée comme un substrat neuronal impliqué dans la dépression majeure, explicable notamment par son rôle dans le traitement de la saillance, l'intéroception, l'évaluation des stimuli/événements émotionnels et le contrôle des interférences dans un contexte affectif. En effet, des études en neuroimagerie ont rapporté une activation anormale (hyper- et hypoactivité) de l'insula lors de tâches d'évaluations de stimuli affectifs (268-270), d'inhibition émotionnelle (271) et de conscience interoceptive (272, 273) chez les sujets atteints de dépression majeure. D'ailleurs, les symptômes somatiques caractéristiques d'une dépression majeure, tels que la perte d'appétit, pourraient être associés à un dysfonctionnement de l'intégration des signaux intéroceptifs dans l'insula. D'autre part, la communication entre le réseau du mode par défaut et le réseau central exécutif, régie en partie par l'insula antérieure dorsale au sein du réseau de saillance, semble particulièrement altérée chez cette population (274, 275). Ainsi, la neurostimulation de l'insula pourrait s'avérer un traitement alternatif intéressant dans le cadre de troubles psychiatriques comme la dépression majeure.

6. Conclusion

Les découvertes qui découlent de ces quatre études permettent de préciser la nature de la contribution de l'insula au traitement de l'information saillante, ainsi qu'à une meilleure compréhension des conséquences neuropsychologiques d'une ablation unilatérale insulaire sur le traitement sensoriel et affectivo-cognitif. Les deux premières études, menées en EEG intracrânienne auprès de patients avec des électrodes implantées dans l'insula pour l'investigation du foyer épileptogène en vue d'une chirurgie d'épilepsie, suggèrent que l'insula contribue au traitement attentionnel pour l'information sensorielle visuelle et auditive. Ainsi, l'insula antérieure participe au déploiement attentionnel volontaire de type *top-down*, alors que la portion postérieure est impliquée dans l'attention automatique de type *bottom-up*. Les deux études suivantes menées en évaluations comportementales auprès de patients ayant subi une insulectomie, quant à elles, mettent en lumière des perturbations sensorielles et d'interférence émotionnelle suivant une chirurgie d'épilepsie insulaire unilatérale. Sur le plan clinique, l'ensemble des résultats de ces travaux conduit à une réflexion sur la pertinence de développer des outils standardisés dans le cadre d'évaluations neuropsychologiques menées auprès de patients chez qui une atteinte insulaire est suspectée ou connue, ainsi que dans le cadre d'évaluations pré- et post-chirurgies d'épilepsie insulaire afin d'appuyer la localisation du foyer épileptogène et d'anticiper les séquelles sensorielles et affectivo-cognitives à la suite de cette intervention. À plus large échelle, cette thèse ouvre la voie à la compréhension de certaines pathologies dans lesquelles l'insula pourrait être directement impliquée.

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Annexes

Tableau 1. – MMN (150-250 ms) responses to target and novel stimuli during the passive auditory oddball task.

Tableau 2. – P100 (50-150 ms) responses to target, novel, and standard stimuli during the visual oddball task.

Tableau 3. – Theta modulations (4-7 Hz; 200-400 ms) recorded in the insula in response to target stimulus during the visual oddball task.

Figure 1. – Average theta activity of anterior insular significant contacts, relative to baseline across conditions (red: target, blue: novel and green: standard).

Tableau 1. – MMN (150-250 ms) responses to target and novel stimuli during the passive auditory oddball task

Pt. #	Anterior insula						Posterior insula					
	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison
1	u11	Left	as-aps	-	-	-						
	u12	Left	as	-	-	-						
	u13	Left	as	-	-	-						
	u31	Left	as	-	-	-						
	u32	Left	as	-	-	-						
	u52	Left	as	-	-	-						
2							u32	Left	al	-	-	-
							u33	Left	al	-	-	-
							u34	Left	al	-	-	-
3	u11	Left	as-ia	-	-	-	u31	Left	pcs	-	-	-
	u12	Left	as	-	-	-	u32	Left	pcs	-	-	-
	u21	Right	as-ms	-	-	-	u33	Left	al	-	-	-
							u34	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
4	u11	Right	ms	-	-	-						
	u12	Right	ms	-	-	-						
	u13	Right	ms	-	-	-						
	u14	Right	ms	-	-	-						
	u15	Right	ms	-	-	-						
	u21	Right	ms	-	-	-						
	u22	Right	ms	-	-	-						
	u23	Right	ms	-	-	-						
5	u13	Left	as	-	-	-	u31	Left	al	-	-	-
	u14	Left	as	-	-	-	u32	Left	al	-	-	-
	u16	Left	as	-	-	-	u33	Left	al	-	-	-
	u17	Left	as	-	-	-	u34	Left	pl	-	-	-

	u35	Left	ms	-	-	-						
	u36	Left	as	-	-	-						
6	u11	Left	sis	-	-	-						
	u12	Left	ms-sis	-	-	-	u31	Left	cs	-	-	-
	u13	Left	ms-sis	-	-	-	u32	Left	cs-li	-	-	-
	u21	Right	as-ia	-	-	-	u33	Left	al	-	-	-
	u22	Right	ms-sis	-	-	-	u34	Left	al	-	-	-
	u23	Right	ms-sis	-	-	-	u35	Left	al	-	-	-
							u36	Left	al	-	-	-
							u37	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
							u45	Right	al	-	-	-
							u46	Right	al	-	-	-
7							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
8	u22	Right	as	-	-	-						
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						

Abbreviations. T = Target; S = Standard; N = Novel; n.s = non significant; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the MMN interval in comparison to baseline are identified with a '-'sign.

Tableau 2. – P100 (50-150 ms) responses to target, novel, and standard stimuli during the visual oddball task

Pt. #	Anterior insula						Posterior insula					
	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison	Contact	Hemisphere	Gyrus	P300 latency	P300 amplitude	Comparison
1	u11	Left	as-aps	-	-	-						
	u12	Left	as	-	-	-						
	u13	Left	as	-	-	-						
	u31	Left	as	-	-	-						
	u32	Left	as	-	-	-						
	u52	Left	as	-	-	-						
2							u32	Left	al	-	-	-
							u33	Left	al	-	-	-
							u34	Left	al	-	-	-
3	u11	Left	as-ia	-	-	-	u31	Left	pcs	-	-	-
	u12	Left	as	-	-	-	u32	Left	pcs	-	-	-
	u21	Right	as-ms	-	-	-	u33	Left	al	-	-	-
							u34	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
4	u22	Right	as	-	-	-	u42	Right	pl	-	-	-
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						
5	u13	Left	as	-	-	-	u31	Left	al	-	-	-
	u14	Left	as	-	-	-	u32	Left	al	-	-	-
	u15	Left	as	-	-	-	u33	Left	al	-	-	-
	u16	Left	as	-	-	-	u34	Left	pl	-	-	-
	u17	Left	as	-	-	-						
	u35	Left	ms	-	-	-						
	u36	Left	as	-	-	-						
6	u11	Left	sis	-	-	-	u31	Left	cs	-	-	-

	u12	Left	ms-sis	-	-	-	u32	Left	cs-li	-	-	-
	u13	Left	ms-sis	-	-	-	u33	Left	al	-	-	-
	u21	Right	as-ia	-	-	-	u34	Left	al	-	-	-
	u22	Right	ms-sis	-	-	-	u35	Left	al	-	-	-
	u23	Right	ms-sis	-	-	-	u36	Left	al	-	-	-
							u37	Left	al	-	-	-
							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
							u43	Right	al	-	-	-
							u44	Right	al	-	-	-
							u45	Right	al	-	-	-
							u46	Right	al	-	-	-
7							u41	Right	al	-	-	-
							u42	Right	al	-	-	-
8	u22	Right	as	-	-	-						
	u23	Right	as	-	-	-						
	u24	Right	as	-	-	-						

Abbreviations. T = Target; S = Standard; N = Novel; n.s = non significant; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

Waveforms showing no significant activity in the P100 interval in comparison to baseline are identified with a '-'sign.

Tableau 3. – Theta modulations (4-7 Hz; 200-400 ms) recorded in the insula in response to target stimulus during the visual oddball task

Pt. #	Anterior insula					Posterior insula				
	Contact	Hemisphere	Gyrus	Comparison	Timing (ms)	Contact	Hemisphere	Gyrus	Comparison	Timing (ms)
1	u11	Left	as-aps	-	-					
	u12	Left	as	-	-					
	u13	Left	as	-	-					
	u31	Left	as	-	-					
	u32	Left	as	-	-					
	u52	Left	as	-	-					
2						u32	Left	al	-	-
						u33	Left	al	-	-
						u34	Left	al	-	-
3	u11	Left	as-ia	-	-	u31	Left	pcs	-	-
	u12	Left	as	-	-	u32	Left	pcs	-	-
	u21	Right	as-ms	-	-	u33	Left	al	-	-
						u34	Left	al	-	-
						u41	Right	al	-	-
						u42	Right	al	-	-
						u43	Right	al	-	-
						u44	Right	al	-	-
4	u22	right	as	T>S	200-400 ms	u42	right	pl	T>S	200-400 ms
	u23	Right	as	T>S	200-400 ms					
	u24	Right	as	T>S	200-400 ms					
5	u13	Left	as	T>S	300-400 ms	u31	Left	al	-	-
	u14	Left	as	T>S	300-400 ms	u32	Left	al	-	-
	u16	Left	as	T>S	300-400 ms	u33	Left	al	T>S	300-400 ms
	u17	Left	as	T>S	200 ms	u34	Left	pl	-	-
	u35	Left	ms	T>S	300 ms					
	u36	Left	as	-	-					
6	u11	Left	sis	-	-	u31	Left	cs	-	-

	u12	Left	ms-sis	-	-	u32	Left	cs-li	-	-
	u13	Left	ms-sis	-	-	u33	Left	al	-	-
	u21	Right	as-ia	-	-	u34	Left	al	-	-
	u22	Right	ms-sis	-	-	u35	Left	al	-	-
	u23	Right	ms-sis	T>S	300-400 ms	u36	Left	al	-	-
						u37	Left	al	-	-
						u41	Right	al	-	-
						u42	Right	al	-	-
						u43	Right	al	-	-
						u44	Right	al	-	-
						u45	Right	al	-	-
						u46	Right	al	-	-
7						u41	Right	al	-	-
						u42	Right	al	-	-
8	u22	Right	as	T>S	200-400 ms					
	u23	Right	as	T>S	200-400 ms					
	u24	Right	as	T>S	200-400 ms					

Abbreviations. T = Target; S = Standard; N = Novel; as = anterior short insular gyrus; aps = anterior peri-insular sulcus; al = anterior long insular gyrus; ms = middle short insular gyrus; ps = posterior short insular gyrus; pl = posterior long insular gyrus; ia = insular apex; pcs = post-central sulcus; sis = short insular sulcus; cs = central sulcus of the insula; li = limen insulae

All significant contacts showed a p-value < 0.01.

Figure 1. – Average theta activity of significant anterior insular contacts, relative to baseline across conditions (red: target, blue: novel and green: standard).