UNIVERSITE DE LILLE - ÉCOLE DOCTORALE BIOLOGIE ET SANTÉ

Thèse d'Université

ÉTUDE DU RÉSEAU DE SAILLANCE DANS LA SURVENUE DES EXPERIENCES INTRUSIVES DANS LA SCHIZOPHRÉNIE ET LE PSYCHOTRAUMA

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Résumé

Les êtres humains doivent être capables d'intégrer de nombreux stimuli perceptifs mais également de filtrer en priorité les seules informations dignes d'intérêt. Ces stimuli sont priorisés en fonction de leur saillance. Le réseau cérébral de la saillance est composé de l'insula antérieure, du cortex cingulaire antérieur dorsal, de l'amygdale, du striatum ventral, et de la substance noire/aire tegmentale ventrale. Ce réseau focalise l'attention et facilite l'accès à la mémoire de travail une fois qu'un évènement saillant est détecté. Le réseau de saillance joue ainsi un rôle crucial dans la balance cognitive entre stimuli externes et processus mentaux internes. De nombreuses études ont démontré l'existence de liens entre ce réseau et le stress. De même, le réseau de saillance a été impliqué dans de nombreuses pathologies psychiatriques ou neurologiques, dont la démence fronto-temporale, les troubles de l'humeur et anxieux, la schizophrénie, les addictions ou encore la douleur. Plus spécifiquement, une implication du réseau de saillance dans les expériences intrusives a été suggérée, notamment au cours des hallucinations dans la schizophrénie, et potentiellement lors des reviviscences post-traumatiques dans le trouble de stress post-traumatique. L'objectif de ce travail de thèse était d'étudier plus précisément le rôle du réseau de saillance dans les phénomènes intrusifs dans ces deux pathologies. Une première partie est consacrée à l'étude des hallucinations dans la schizophrénie, et une seconde porte sur l'étude des reviviscences post-traumatiques dans le trouble de stress post-traumatique. Nous avons tout d'abord étudié les bases neurales de la saillance dans la schizophrénie, en réalisant une méta-analyse basée sur les coordonnées fonctionnelles (en imagerie par résonance magnétique) d'études se focalisant sur les processus de récompense. Nous avons

ainsi montré que l'hypoactivation du striatum ventral retrouvée chez les patients souffrant de schizophrénie lors de ces tâches était corrélée aux symptômes positifs du trouble. Plusieurs études 'trait' et 'état' ont proposé que le réseau de saillance puisse jouer un rôle modulateur dans les expériences hallucinatoires. Dans une deuxième étude, nous avons donc validé une méthode de capture hallucinatoire à même de comparer le décours temporel des aires hyperactivées dans ces expériences, avec celui des différents réseaux fonctionnels de repos, étape indispensable pour la mesure dynamique du réseau de saillance dans ces phénomènes. Enfin, dans une troisième étude, nous avons étudié le rôle joué par le réseau de saillance, et en particulier de l'insula antérieure, dans la réponse au traitement dans le trouble de stress post-traumatique. En effet, les bases neurales de la réponse au traitement sont encore peu connues, notamment via des mesures de connectivité effective. Nous avons ainsi pu montrer l'importance du rôle modulateur de l'insula antérieure dans la diminution des reviviscences post-traumatiques. Ces résultats laissent entrevoir plusieurs applications concrètes en psychiatrie. En particulier, l'amélioration des connaissances physiopathologiques des phénomènes intrusifs, à la fois dans la schizophrénie et le trouble de stress post-traumatique, avec la perspective de développer des méthodes de capture des reviviscences post-traumatiques sur le modèle de la capture hallucinatoire, ouvre des possibilités d'avancées dans le champ de la médecine personnalisée dans ces deux pathologies.

Title: Salience network and intrusive experiences in schizophrenia and post-traumatic stress disorder

Abstract

In a sensorially complex world, human beings need to efficiently and effectively filter and respond to relevant stimuli. Stimuli are prioritized according to their saliency. Especially, the salience network is readily identified as an intrinsically connected large-scale network including prominent nodes as the anterior insula, the dorsal anterior cingulate cortex, the amygdala, the ventral striatum, and the substantia nigra/ventral tegmental area. The salience network not only plays an important role in saliency detection and reactivity but also facilitates access to attention and working memory resources once a salient event has been detected. Stress reactions have been previously linked to activation of the salience network. Moreover, network models are now being widely used to characterize deficits in a wide range of psychiatric and neurological disorders. These studies have provided evidence for prominent salience network dysfunctions in frontotemporal dementia, mood and anxiety disorders, schizophrenia, drug addiction, or pain. Especially, the role of the salience network in intrusive experiences has been suggested, during hallucinations in patients with schizophrenia, and more recently, during re-experiencing in patients suffering from post-traumatic stress disorders. The goal of the present thesis is to improve knowledge about the role of the salience network in intrusive thoughts in these two disorders. In a first part, we studied the role of the salience network in hallucinations in patients with schizophrenia. In a second part, we studied its role in re-experiencing in post-traumatic stress disorder. In a

coordinate-based meta-analysis, we explored the neural bases of salience in schizophrenia, focusing on reward processing. We showed that the hypoactivation of the ventral striatum found in patients with schizophrenia during such tasks was correlated with positive symptoms of schizophrenia. Furthermore, several 'trait' and 'state' studies found that the salience network has a modulatory function in the occurrence of hallucinatory experiences. In a second study, we thus validated a method for hallucinations' capture, making possible the comparison between the time-course of brains areas overactivated during these experiences and conventional resting-state networks, which is a mandatory step for the study of the dynamic role of the salience network during hallucinations. Finally, in a third study, we explored the role of insular cortex in re-experiencing symptoms in post-traumatic stress disorders, and especially its role in response to pre-reactivation propranolol therapy. The neural bases of treatment-response are indeed still poorly understood, notably via effective connectivity analysis. We showed that the anterior insula exerted causal influences over the brain which correlate with reexperiencing in post-traumatic stress disorder. These studies pave the way for future developments. Especially, improvement in the knowledge about the physiopathology of intrusive experiences, both in schizophrenia and post-traumatic stress disorder, are important to develop re-experiencing capture methods, and for the development of personalized medicine in these two disorders.

Mots clés : imagerie cérébrale, réseau de saillance, psychiatrie, schizophrénie, trouble de stress post-traumatique, intrusion

Key words: brain imaging, salience network, psychiatry, shizophrenia, post-traumatic stress disorder, intrusion

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Liste des abréviations

CEN : Central Executive Network/Réseau exécutif central

DMN : Default Mode Network/Réseau du mode par défaut

EMDR : Eye Movement Desensitization and Reprocessing/Désensibilisation et retraitement par les mouvements oculaires

GABA : Gamma-aminobutyric acid/Acide γ-aminobutyrique

IRM : Imagerie par Résonnance Magnétique

IRMf : Imagerie par Résonnance Magnétique fonctionnelle

LCS : Liquide Cérébro-Spinal

MDMA : Méthylènedioxyméthamphétamine

PANSS : Positive And Negative Syndrome Scale

rTMS : repetitive Transcranial Magnetic Stimulation (rTMS)/Stimulation magnétique transcrânienne répétée

SN : Salience Network/Réseau de saillance

TEP-scan : Tomographie par Emission de Positons

TSPT : Trouble de Stress Post-Traumatique

I. Introduction

1) Définition du concept de saillance

Dans un environnement rempli de stimuli sensoriels complexes, les organismes vivants doivent être capables de choisir et répondre de manière efficace aux stimuli d'intérêt, pour déterminer s'ils sont par exemple en présence d'un ami, d'un prédateur ou d'une proie. Il en est de même pour les êtres humains, qui doivent être capables d'intégrer de nombreuses informations perceptives, alors que les capacités d'intégration physique et motrice sont limitées. En effet, séparer un stimulus d'intérêt des autres nécessite de solliciter des ressources attentionnelles (Posner & Petersen, 1990), de filtrage, d'orientation sensorielle et comportementale, de motivation, de sélection de l'action à effectuer, et enfin d'exécution (Redgrave et al., 2011). Pour permettre cette sélection, les stimuli sont priorisés en fonction de leur 'saillance'. Un évènement est tout simplement défini comme saillant quand il doit être priorisé par rapport aux autres évènements qui surviennent dans un contexte donné (Winton-Brown et al., 2014). Cela sous-entend que les caractéristiques des différents stimuli sont comparées entre elles. Par exemple, dans le cas de la vision, certaines caractéristiques peuvent être considérées comme saillantes (Nothdurft, 2000) : la luminosité, le mouvement, la couleur, le contraste, et l'orientation sont additionnés pour déterminer quels sont les éléments qui doivent attirer l'attention. La saillance est souvent considérée comme ayant une bonne reproductibilité interpersonnelle, mais elle peut tout de même être influencée par des facteurs internes comme le but à atteindre, les croyances et l'histoire personnelle des sujets. Par ailleurs, la saillance présente de multiples facettes que sont la saillance

émotionnelle, dirigée vers un but, motivationnelle, physique, ou médiée par la nouveauté (Cf. **Figure 1**) (Winton-Brown et al., 2014).

Figure 1. La saillance est multidimensionnelle et signalée (en partie) par des décharges dopaminergiques (Winton-Brown et al., 2014).

Sur le plan neurobiologique, la priorisation d'un évènement (qui est alors déterminé comme saillant), est intimement liée à la survenue de décharges dopaminergiques dans plusieurs structures cérébrales. En particulier, le modèle de récompense, définie comme la valeur positive donnée à un objet, un comportement, ou un état interne (Haber, 2003), a été très largement étudié sous cet angle. Les addictions (définies comme un dérèglement du système de récompense) ont par exemple pu être liées aux effets pharmacologiques des substances psychoactives agissant via une augmentation ou un prolongement de l'action de la dopamine sur ses cibles d'action principales (Wise & Hoffman, 1992). De même, la plupart des récompenses sont rendues ineffectives chez les animaux chez qui le système dopaminergique serait bloqué (Wise, 2004). Plusieurs études électrophysiologiques ont d'ailleurs montré que l'on observait au niveau des neurones dopaminergiques des décharges

phasiques de latence courte lorsqu'il existait une différence entre la récompense obtenue et la récompense prédite (Schultz, 1998, 2010, 2013; Schultz et al., 2008).

2) Rôle du réseau de saillance

Sur le plan neuroanatomique, le réseau de saillance, également appelé salience network (SN) est un réseau de repos intrinsèquement connecté à large échelle, principalement composé de l'insula antérieure, et du cortex cingulaire antérieur dorsal (Menon, 2015). Il inclut également trois structures sous-corticales : l'amygdale, le striatum ventral, et la substance noire/aire tegmentale ventrale (Cf. **Figure 2**).

Ce réseau a pu être étudié en mesurant l'activation cérébrale des régions d'intérêt, mais également dans des études de connectivité. En effet, l'étude approfondie des interactions entre les régions cérébrales est importante pour comprendre les circuits cérébraux impliqués dans les pathologies (Friston, 2002). La connectivité fonctionnelle, consiste dans la mesure de la corrélation entre le décours temporel de différentes régions cérébrales (Friston, Frith, Liddle, et al., 1993). Cependant, la connectivité fonctionnelle ne permet pas de connaître les interactions directes qui génèrent ces corrélations. La connectivité effective, qui est définie par l'influence d'un système neuronal sur un autre (Friston, Frith, & Frackowiak, 1993; Friston, Frith, Liddle, et al., 1993), a pour but de répondre à ce problème en utilisant des méthodes statistiques modélisant les interactions neuronales directes.

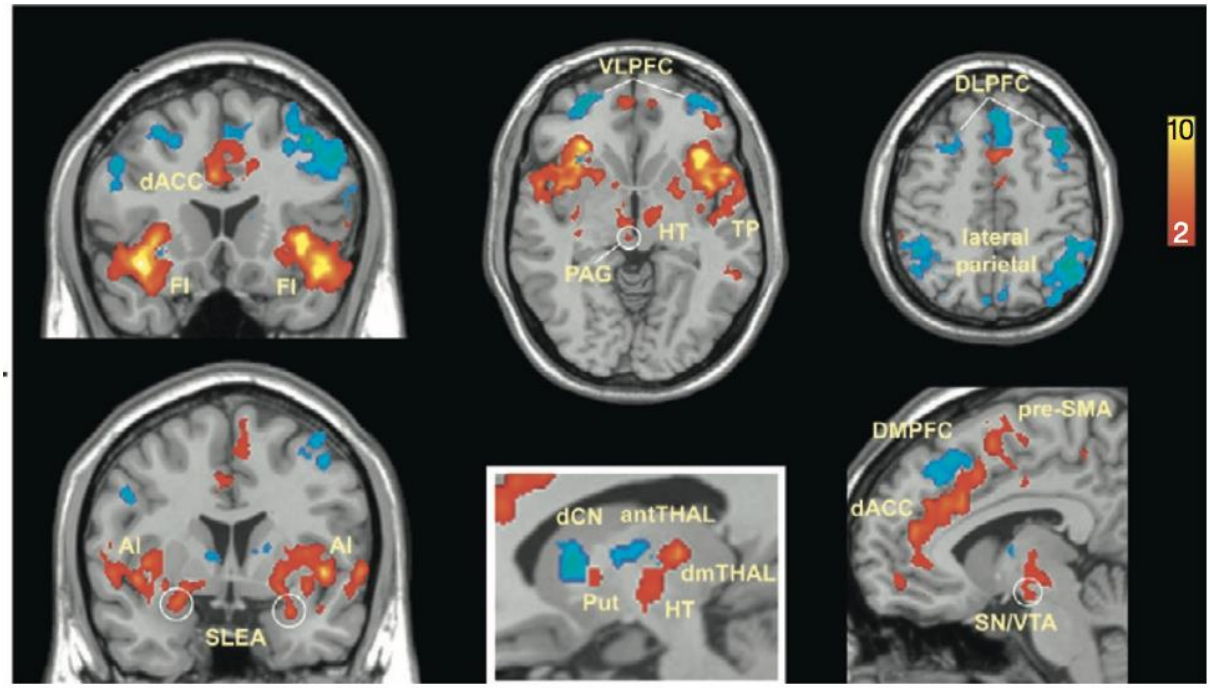


Figure 2. Identification du réseau de saillance (SN) en utilisant une analyse en composante indépendante (Menon, 2015). Régions corticales et sous-corticales (en rouge) du réseau de saillance. Le réseau de saillance a des profils distincts de connectivité fonctionnelle intrinsèque corticale et sous-corticale allant du réseau central exécutif frontopariétal latéral au thalamus antérieur (antTHAL), noyau caudé dorsal (dCN), thalamus dorsomédial (dmTHAL), hypothalamus (HT), substance grise périaqueducale (PAG), putamen (Put), amygdale étendue sublenticulaire (SLEA), substance noire/aire tegmentale ventrale (SN/VTA), et pôle temporal (TP). dACC : cortex cingulaire antérieur dorsal ; FI : cortex fronto-insulaire orbital ; VLPFC : cortex préfrontal ventrolatéral ; DLPFC : cortex préfrontal dorsolatéral ; AI : insula antérieure ; DMPFC : cortex préfrontal dorsomédial ; pre-SMA : aire prémotrice supplémentaire.

De nombreuses études d'imagerie cérébrale ont impliqué le SN dans des processus cognitifs et affectifs variés, tels que la communication, le comportement social, et la conscience de soi via l'intégration d'information sensorielles, émotionnelles et cognitives (Craig, 2009; Gogolla et al., 2014; Menon & Uddin, 2010). En particulier, l'insula antérieure semble impliquée plus spécifiquement dans la détection et l'intégration des stimuli d'intérêt (Cf. **Figure 3**). Elle reçoit ainsi des afférences convergentes issues de multiples modalités sensorielles impliquant les systèmes auditifs et visuels (Augustine, 1996; Bamiou et al., 2003; Butti & Hof, 2010; Mesulam & Mufson, 1982; Nieuwenhuys, 2012), et plusieurs études suggèrent son implication dans l'attention simultanée vers des stimuli multisensoriels (Bushara et al., 2001, 2003). L'insula est également soumise à de multiples influences du système nerveux autonome, telles que les battements cardiaques, la conductance cutanée et la respiration (Critchley et al., 2013; Singer et al., 2009). Ces processus autonomes ont été reliés à la captation par la conscience des évènements saillants et impliquent probablement des interactions avec l'insula postérieure. Le cortex cingulaire antérieur dorsal est quant à lui plus directement impliqué dans la sélection des réponses et la gestion des conflits (Ide et al., 2013). Ainsi, l'insula antérieure recevrait des informations multisensorielles spécifiques utiles aux cortex cingulaire antérieur dorsal et préfrontal dorsomédial qui lui sont associé (Averbeck & Seo, 2008; Vogt & Pandya, 1987). A l'inverse, ces dernières régions enverraient de nombreuses efférences vers les régions motrices. De plus, le cortex cingulaire antérieur et le cortex préfrontal dorsomédial ont des connections directes avec la moelle épinière et les régions oculomotrices sous-corticales (Fries, 1984), exerçant un contrôle direct sur l'action.

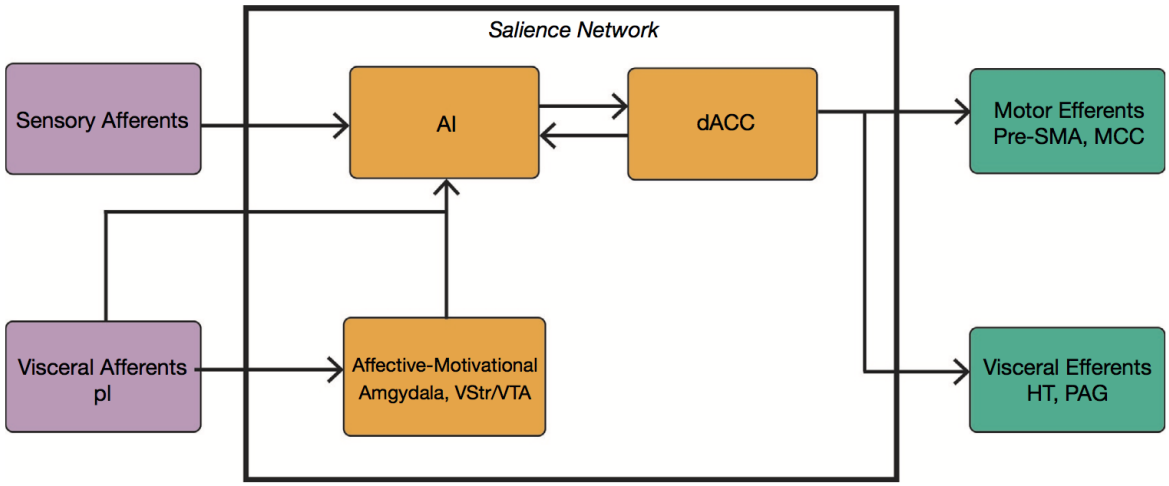


Figure 3. Organisation du réseau de saillance et ses relations avec ses afférences et efférences principales (Menon, 2015). L'insula antérieure reçoit des informations multisensorielles convergentes, des signaux affectifs et motivationnels, et des afférences viscérales, reflétant la saillance biologique et la demande cognitive. A l'inverse, le cortex cingulaire antérieur dorsal joue un rôle dans la sélection de la réponse, le guidage des comportements et la modulation de la réactivité autonome. AI : insula antérieure ; dACC : cortex cingulaire antérieur dorsal, HT : hypothalamus ; PAG : substance grise périaqueducale ; pI : insula postérieure ; VStr : striatum ventral ; VTA : aire tegmentale ventrale.

Le SN ne joue pas seulement un rôle dans la détection de la saillance et la réactivité. En effet, il facilite également l'accès à l'attention et à la mémoire de travail une fois qu'un évènement saillant a été détecté. Le SN joue ainsi un rôle crucial dans la balance entre les réseaux cérébraux à large échelle impliqués dans l'attention orientée vers les stimuli externes et les processus mentaux internes (Cf. **Figure 4**) (Sridharan et al., 2008). Ainsi, au cours de tâches ayant une charge cognitive importante, le SN est activé concomitamment au réseau exécutif central (CEN), alors que le réseau du mode par défaut (DMN) montre une

diminution de son métabolisme en dessous du niveau de base (Greicius et al., 2003, 2004; Raichle et al., 2001). De cette façon, les réponses cérébrales de ces régions augmentent et diminuent proportionnellement et souvent de manière antagoniste, en relation à des demandes cognitives spécifiques et à la difficulté des tâches. Une fois qu'un évènement saillant est détecté, l'insula antérieure facilite ce processus en initiant un signal de transition qui engage le système de contrôle cognitif et désengage le DMN (Sridharan et al., 2008). L'étude de patients avec lésion cérébrale semble confirmer cette fonction du SN. Bonnelle et coll. ont ainsi pu montrer qu'une fonction anormale du DMN était prédite de manière spécifique par le niveau d'altération de la substance blanche des faisceaux connectant l'insula antérieure droite au cortex cingulaire antérieur dorsal et à l'aire motrice pré-supplémentaire (Bonnelle et al., 2012). Ainsi ces résultats mettent en évidence que l'intégrité du SN est nécessaire pour réguler de manière efficiente l'activité du DMN, et que son altération mène à un contrôle cognitif inefficient et des performances cognitives plus faible dans les tâches de contrôle cognitif. De manière générale, ces mécanismes de balance entre les réseaux cérébraux intrinsèques (également dits « de repos ») aident à focaliser l'attention sur les stimuli et les objectifs d'intérêt, et en conséquence, ils jouent un rôle important dans le mécanisme de saillance (Menon & Uddin, 2010).

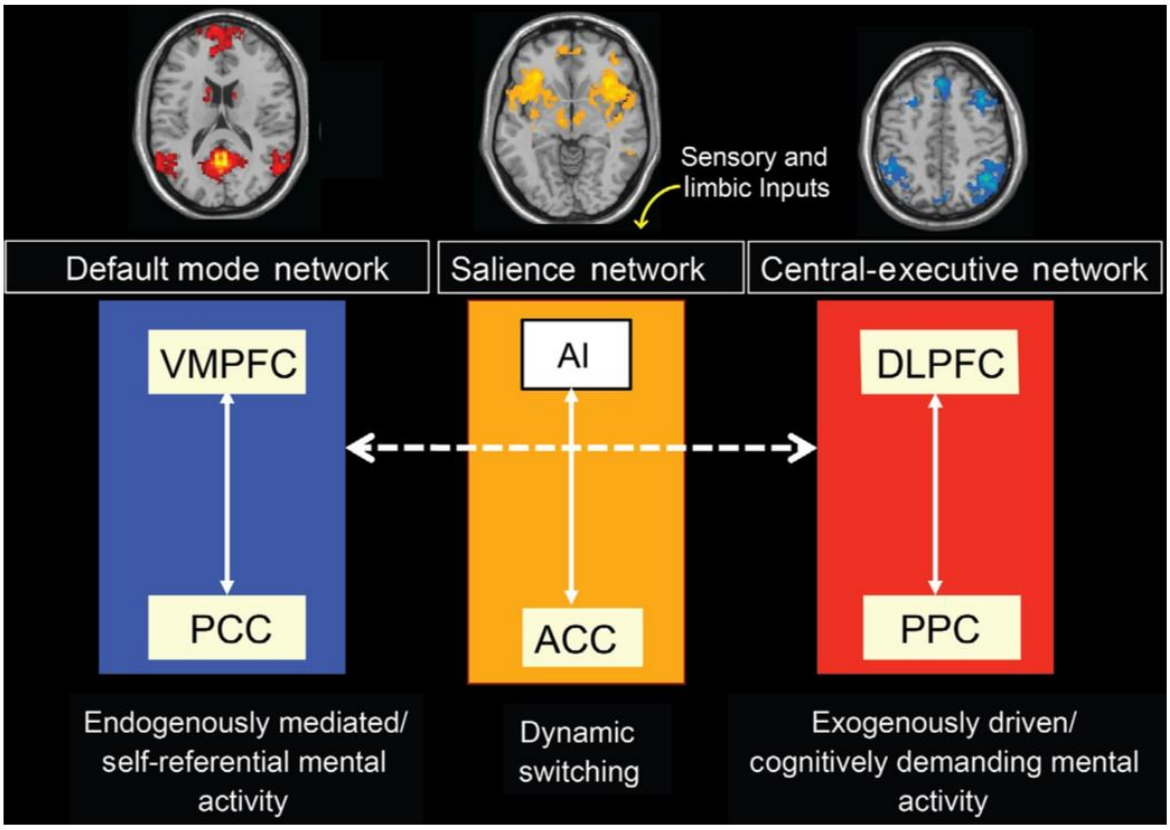


Figure 4. Balance dynamique entre les réseaux à large échelle médiée par le réseau de saillance (Menon, 2015). Le réseau de saillance (SN) joue un rôle central dans la balance entre le réseau central exécutif (CEN) et le réseau du mode par défaut (DMN). Le SN recrute les régions exécutives centrales et impliquées dans le contrôle des tâches pour maintenir le processus cognitif et manipuler l'information dans la mémoire de travail en supprimant l'activité du DMN pour maintenir l'attention focaliser sur les objectifs liés à la réalisation d'une tâche.

3) Liens entre stress et SN

Le SN semble également directement lié au stress, en particulier via le système B-adrénergique. Notamment, le locus coeruleus est une région cérébrale localisée au niveau du tronc cérébral, source principale d'épinéphrine dans le cerveau, et donc directement impliqué dans les réactions au stress. Cette structure envoie des efférences dans presque tout le cerveau. La dysrégulation de ce système a été impliquée dans de nombreuses pathologies psychiatriques incluant la dépression, l'anxiété, le trouble déficit de l'attention avec ou sans hyperactivité, le trouble de stress post-traumatique, et les pathologies neurodégénérative (Bangasser et al., 2019; Fortress et al., 2015; Isingrini et al., 2016; Weinshenker, 2018). Le lien entre système B-adrénergique et SN a été retrouvé dans de nombreuses études, en particulier dans un modèle murin, dans lequel l'activation du locus coeruleus a été associée à une activation du SN (Zerbi et al., 2019).

De même, des études d'imagerie cérébrale chez l'humain (Cousijn et al., 2010; Oei et al., 2012; van Marle et al., 2009) ont montré une hyperactivation de l'amygdale, après l'induction expérimentale de stress. L'hyperactivation des régions limbiques et de régions sous-corticales incluant l'amygdale, sont fréquemment observées après la provocation de symptômes chez les sujets ayant subi un psychotraumatisme (Osuch et al., 2008). L'administration de médicaments entraînant une élévation des niveaux d'épinéphrine a reproduit ces effets (Onur et al., 2009), en particulier lorsque cela était accompagné d'une administration d'hydrocortisone (Kukolja et al., 2008). Enfin, la réalisation d'une délétion fonctionnelle sur le gène codant pour les récepteurs présynaptiques adrénergiques alpha2b,

qui réduisent le feedback négatif au sein du système noradrénergique, entraînait également une augmentation de l'activité amygdalienne induite par le stress (Cousijn et al., 2010).

L'activité dans d'autres régions du SN, comme le cortex cingulaire antérieur dorsal et l'insula antérieure, a été associée de manière reproductible aux marqueurs physiologiques du stress, comme l'augmentation de la fréquence cardiaque (Wager et al., 2009), l'augmentation de la tension artérielle (Gianaros et al., 2008), la réduction de la variabilité cardiaque (Ahs et al., 2009), et l'augmentation des niveaux de cortisol.

De manière plus générale, la connectivité globale du SN a été corrélée à de multiples mesures physiologiques et psychologiques du stress (Hermans et al., 2011). L'hypothèse du rôle causal de l'épinéphrine a été renforcée par le fait que la connectivité fonctionnelle du SN était diminuée après administration de propranolol, qui est un antagoniste B adrénergique, alors que l'inhibition de la synthèse des corticostéroïdes ne montrait pas d'effet (Hermans et al., 2011). De même, l'administration d'un agoniste noradrénergique était associée à une hyperactivation du SN (Cameron & Minoshima, 2002). Immédiatement après une exposition à un stress, les régions du SN montraient enfin une connectivité fonctionnelle augmentée entre l'amygdale et les autres régions du SN (van Marle et al., 2010).

Pour étudier cette réaction au stress, le « modèle de peur » a été particulièrement utilisé, en particulier pour l'étude du trouble de stress post-traumatique (TSPT). Apprendre à correctement prédire une menace (conditionnement à la peur ou à la menace) est fondamental pour la survie, mais apprendre à éteindre ces mêmes signaux de peur

(extinction de la peur ou de la menace) est tout autant fondamental. Dans les troubles anxieux, des déficits d'extinction de la peur ont été largement rapportés (Duits et al., 2015). Le traitement de première intention dans le TPST est la thérapie d'exposition. Elle a pour objectif de favoriser ce processus. Cette théorie a été confortée par plusieurs études en imagerie cérébrale, montrant que l'activation cérébrale durant l'apprentissage de l'extinction de la peur pouvait prédire l'amélioration clinique après thérapie d'exposition chez des patients présentant une anxiété sociale (Ball et al., 2017). Dans une méta-analyse récente (Fullana et al., 2018), les régions impliquées dans l'extinction de peur comprenaient les régions du SN (cortex cingulaire antérieur rostro-dorsal, insula antérieure bilatérale s'étendant à l'operculum frontal) et des régions impliquées dans le contrôle sensorimoteur (cortex prémoteur supplémentaire, thalamus antérieur et médial). Les régions impliquées dans le contrôle moteur, et en particulier le cortex précentral, ont d'ailleurs été impliquées dans les comportements de défense chez les animaux (Graziano & Cooke, 2006). Elles pourraient sous-tendre les réactions de type « fight ot flight » fréquemment retrouvées lors des situations de stress survenant dans des contextes psychotraumatiques. D'autres régions ont été impliquées comme le cortex préfrontal médial, le cortex préfrontal dorsolatéral, le putamen antérieur s'étendant au noyau caudé ventral, le pallidum ventral bilatéral, et la substance grise périaqueducale. Le SN semble donc être largement impliqué dans l'extinction de la peur.

4) Implication du SN dans les pathologies psychiatriques

Le SN a été impliqué dans de nombreuses pathologies psychiatriques ou neurologiques, dont la démence fronto-temporale, les troubles de l'humeur et anxieux, la schizophrénie, les addictions, ou encore la douleur (Menon, 2011). Une méta-analyse de données en imagerie structurale impliquant plus de 7000 sujets souffrant de pathologies psychiatriques a mis en évidence l'importance du SN dans des troubles aussi variés que la dépression, le trouble bipolaire, la schizophrénie, les troubles liés à l'usage de substance, les troubles obsessionnels compulsifs et les troubles anxieux (Goodkind et al., 2015). Toutes ces pathologies présentaient une atrophie corticale dans le cortex cingulaire antérieur dorsal et le cortex insulaire antérieur bilatéral. En conséquence, une perte de l'intégrité fonctionnelle du SN, et son corollaire clinique, la perte de contrôle cognitif, ont été proposés comme une caractéristique transdiagnostique de nombreux troubles psychiatriques (McTeague et al., 2016). De plus, il a été montré que des lésions isolées de l'insula étaient associées à des dysfonctions du système nerveux autonome touchant à la perception gustative, olfactive, auditive, somatosensorielle, et multimodale, la conscience du corps, le dégoût, l'humeur, la volition ou encore les addictions (Ibañez et al., 2010).

Si les régions cérébrales qui composent le SN sont impliquées dans de nombreuses pathologies psychiatriques, la fonction régulatrice du SN dans la balance entre le DMN et le CEN est également altérée. En effet, une organisation intrinsèque et une connectivité aberrante du SN, du CEN et du DMN est ainsi caractéristique de plusieurs troubles psychiatriques et neurologiques. Le modèle le plus souvent retrouvé (Cf. **Figure 5**) (Menon, 2011) implique une mauvaise détection des évènements saillants. Ce repérage défaillant de

la part du SN entraîne un engagement aberrant du CEN vers des stimuli (internes ou externes) parfois non pertinents, parasitant la cognition et les comportements adaptatifs orientés vers un but. Une organisation aberrante du DMN, associée à un engagement faible ou un désengagement du DMN lié aux évènements saillants est, quant à elle, souvent associée à une altération de l'activité mentale auto-produite (comme pour les hallucinations dans la schizophrénie (Jardri et al., 2013)).

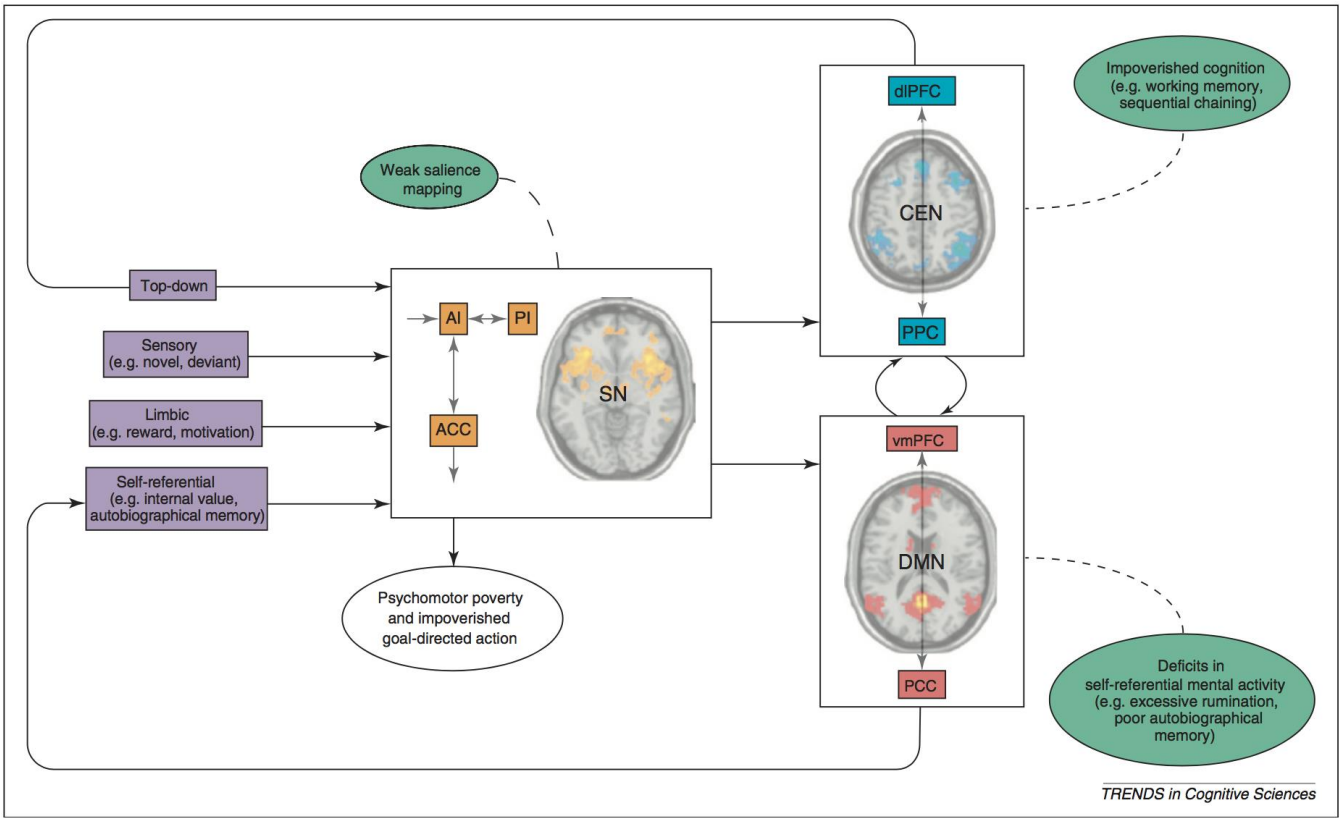


Figure 5. Modèle du « triple réseau fonctionnel » dans les pathologies psychiatriques (Menon, 2011). L'organisation intrinsèque et l'interconnectivité aberrante du réseau de saillance (SN), du réseau exécutif (CEN) et du réseau de conscience par défaut (DMN) sont caractéristiques de nombreux troubles neuropsychiatriques. Ce modèle propose qu'à travers une faible détection de la saillance et une faible cartographie des stimuli d'intérêt et des évènements mentaux internes, le SN jouerait un rôle central dans la psychopathologie et l'émergence de symptômes. Une mauvaise cartographie de la saillance par le SN entraînerait un engagement aberrant du CEN, compromettant la cognition et les comportements adaptatifs. L'organisation aberrante du DMN aussi bien qu'un engagement faible (voir un désengagement) du DMN lié aux évènements saillants serait associée avec une altération de l'activité mentale auto-attribuée.

Parmi les différentes pathologies concernées par ces dysfonctionnements du SN, la schizophrénie occupe une place de choix. La schizophrénie est une pathologie qui touche environ 1 % de la population mondiale (McGrath et al., 2008). Elle est habituellement divisée en 5 dimensions : positive, négative, désorganisation, anxiété/dépression et impulsivité/excitation (Kay & Sevy, 1990). À ce jour, la schizophrénie reste une pathologie très handicapante pour les patients et dont le fardeau à l'échelle mondiale reste majeur. En effet, son apparition, le plus souvent entre 18 et 35 ans, est à l'origine d'un isolement social et professionnel, et d'une perte d'autonomie importante (Guelfi & Rouillon, 2017). De même, cette sous-population présente une surmortalité par rapport à la population générale. Cela peut notamment s'expliquer par un taux de suicide élevé (Hor & Taylor, 2010) et une plus grande fréquence des pathologies respiratoires, cardiovasculaires et infectieuses. Cette surmortalité peut en partie être mise en lien avec les effets des traitements antipsychotiques, en particulier pour les pathologies cardiovasculaires. Les difficultés d'accès aux soins et la stigmatisation de ces patients semblent également un facteur majeur (Wildgust & Beary, 2010).

Différentes études de connectivité ont étudié les dysfonctions du SN dans la schizophrénie. Deux méta-analyses (Dong et al., 2018; O'Neill et al., 2019) ont étudié les anomalies de connectivité du SN dans la schizophrénie. La première (Dong et al., 2018) a mis en évidence que la schizophrénie était caractérisée par une réduction de la connectivité fonctionnelle entre les régions du SN (cortex cingulaire antérieur, insula ou cortex cingulaire moyen), et plusieurs autres régions comme le cortex cingulaire postérieur gauche, le precuneus, le cortex pariétal inférieur, le noyau caudé gauche, le thalamus, le putamen et le cortex cingulaire antérieur. La deuxième a également retrouvé une connectivité

fonctionnelle réduite entre les régions du SN et les régions du DMN et du CEN (O'Neill et al., 2019). Dans cette dernière étude, il a également été montré, en comparant les sujets recevant un traitement antipsychotique et ceux naïfs de traitement, que les traitements médicamenteux diminuaient la connectivité entre le SN et les régions préfrontales. Ces anomalies de connectivité semblent également être présentes dès les stades précoces d'évolution de la maladie. Ainsi, une diminution de l'anti-corrélation entre l'insula antérieure droite et le cortex cingulaire postérieur chez les patients à haut risque et ultra-haut risque d'évolution vers un trouble psychotique a été mise en évidence (Wotruba et al., 2014). Pour mieux comprendre cette dynamique, une étude combinant connectivité fonctionnelle statique et dynamique a montré que la connectivité statique à l'intérieur du SN modulait l'influence de la connectivité dynamique à l'intérieur du SN sur la connectivité entre le SN, le CEN et le DMN (Wang et al., 2016). La modulation du CEN et du DMN par l'insula antérieure droite, étudiée par des méthodes de connectivité effective, semble diminuée dans la schizophrénie, et a été associée à une diminution des performances cognitives (Moran et al., 2013). Une autre étude a révélé que les patients souffrant de schizophrénie montraient une diminution de la connectivité effective de l'insula antérieure droite vers le cortex dorsolatéral droit et le precuneus (Palaniyappan et al., 2013).

Le TPST est le deuxième modèle d'intérêt que nous souhaitons aborder, qui s'avère par ailleurs être également une pathologie fréquente avec une prévalence autour de 1 % (Karam et al., 2014). Cette pathologie peut survenir suite à une exposition à un évènement traumatique (comme les violences interpersonnelles, les combats, les accidents avec mise en jeu du risque vital et les catastrophes naturelles). Les symptômes du TPST incluent des souvenirs intrusifs et stressant du traumatisme, mais également des cauchemars

traumatiques, une irritabilité, une hypervigilance (définie comme un état de sensibilité augmentée à la menace ou une préoccupation augmentée pour un danger potentiel), des difficultés de sommeil, des troubles de concentration et un retrait émotionnel. Les sujets présentant un TPST évitent fréquemment les endroits, les activités ou les choses qui pourraient leur rappeler le psychotraumatisme (American Psychiatric Association, 2013). Ces symptômes particulièrement invalidants sont associés à une plus grande fréquence de nombreuses comorbidités psychiatriques, un retentissement fonctionnel plus important, et une augmentation du risque suicidaire (Lewis et al., 2019). Dans le TSPT, une méta-analyse (Koch et al., 2016) a montré une augmentation de la connectivité fonctionnelle du SN, mais une diminution de la connectivité fonctionnelle du DMN dans le TSPT. Enfin, dans une étude de connectivité effective, trois régions ont été impliquées chez des soldats présentant un TSPT : le gyrus frontal médian, l'insula et l'hippocampe (Rangaprakash et al., 2018). L'influence du gyrus frontal médian sur l'insula était réduite, à l'origine d'une désinhibition par l'insula de l'amygdale et l'hippocampe. Dans une autre étude étudiant la connectivité effective au sein du SN, une diminution du signal de l'amygdale droite vers l'insula droite a été rapportée (Weng et al., 2019).

5) Rôle du SN et expériences intrusives

Les souvenirs intrusifs, les hallucinations, ou encore les ruminations et inquiétudes persistantes sont des caractéristiques centrales dans de nombreuses pathologies telles que le TPST, la schizophrénie, la dépression ou l'anxiété (Brewin et al., 2010; Larøi et al., 2012; Newman et al., 2013; Watkins, 2008).

En moyenne, 70 % des patients souffrant de schizophrénie ont des hallucinations auditives (Andreasen & Flaum, 1991) et l'on estime à 27 % le taux d'hallucinations visuelles (Waters et al., 2014). Ces hallucinations ont un retentissement conséquent avec, en particulier, un risque de suicide augmenté (Hor & Taylor, 2010) et sont à l'origine d'un handicap fonctionnel important. Au-delà des liens connus entre le réseau de saillance et la schizophrénie, certaines études se sont intéressées de manière plus spécifique au rôle du réseau de saillance dans la survenue d'expériences hallucinatoires. Une étude a ainsi spécifiquement étudié la connectivité dans le SN (Manoliu et al., 2014), en comparant les niveaux de connectivité à l'intérieur du SN pour des individus souffrant de psychose en phase de rémission, et des sujets sains. La sévérité des hallucinations était spécifiquement associée de façon négative à la connectivité fonctionnelle de l'insula droite. Une étude incluant 98 sujets a retrouvé une augmentation de la connectivité fonctionnelle entre l'insula gauche et le gyrus frontal inférieur droit chez des patients souffrant d'hallucinations acoustico-verbales (Clos et al., 2014), alors qu'une autre comprenant 54 sujets (Vercammen et al., 2010) incluant des régions d'intérêt situées dans l'insula bilatérale n'a pas retrouvé d'altération de la connectivité. Plus récemment, une étude de connectivité effective de notre équipe a permis de montrer de manière dynamique le rôle du SN au cours des

différentes étapes de l'hallucination, confirmant que le SN joue un rôle crucial dans le switch entre DMN et CEN au cours des expériences hallucinatoires (Lefebvre et al., 2016).

Le TPST est également une pathologie où les expériences intrusives jouent un rôle particulièrement important. Certaines études ont cherché à en étudier la neurobiologie. Dans ce contexte, plusieurs recherches ont suggéré le rôle de l'hyperactivité noradrénergique (Pitman et al., 2012; Pole, 2007), système qui est directement lié au réseau de saillance. Par ailleurs, certaines études en imagerie cérébrale suggèrent une hyperactivation de l'insula et de l'amygdale, associée à une diminution de l'activation du cortex préfrontal médial, lors de la réalisation de tâches émotionnelles comparant sujets souffrant de TPST et sujets sains. Elles suggèrent le rôle de ces régions dans les expériences intrusives du TPST, via une augmentation de la réponse émotionnelle (Yehuda et al., 2015). De même, une étude récente de connectivité fonctionnelle a retrouvé qu'une augmentation de la connectivité de l'amygdale avec le gyrus frontal inférieur était corrélée à la sévérité des reviviscences (McCurry et al., 2020). L'étude de la dynamique des réseaux de repos a montré que la connectivité fonctionnelle entre le DMN, le SN et le CEN était également altérée chez les patients présentant des symptômes intrusifs plus sévères (Zandvakili et al., 2020), et corrélée au degré de stress et d'inflammation de bas grade (Kim et al., 2020). Le CEN a par ailleurs également été impliqué dans les symptômes intrusifs. Notamment, l'augmentation de la connectivité effective du cortex pariétal postérieur gauche vers le cortex dorsolatéral préfrontal gauche, s'est avérée corrélée aux réviviscences post-traumatiques (Weng et al., 2019).

6) Hypothèses générales du travail de thèse

L'objectif de ce travail était donc d'étudier plus précisément le rôle du réseau de saillance dans les phénomènes intrusifs. Une première partie sera consacrée à l'étude des hallucinations dans la schizophrénie, et une seconde sera consacrée à l'étude des reviviscences post-traumatiques dans le TPST.

Tout d'abord, dans une méta-analyse basée sur les coordonnées fonctionnelles, nous avons étudié les bases neurales de la saillance dans la schizophrénie, en se focalisant sur les processus de récompense. Cette étude a également permis d'étudier les corrélations entre les modifications de signal et les symptômes positifs retrouvés dans la schizophrénie, afin de tester l'hypothèse d'une implication du réseau de saillance.

Nous avons vu que plusieurs études 'trait' et 'état' avaient proposé un rôle modulateur du réseau de saillance dans les expériences hallucinatoires. Dans une deuxième étude, nous avons donc validé une méthode de capture hallucinatoire en IRM fonctionnelle, étape indispensable pour la mesure dynamique de l'activité et de la connectivité du réseau de saillance au cours de ces phénomènes.

Enfin, dans une troisième étude, nous avons étudié le rôle joué par le réseau de saillance (et en particulier de l'insula antérieure), dans la réponse au traitement dans le trouble de stress post-traumatique. En effet, les bases neurales de la réponse au traitement sont encore peu connues, notamment via des mesures de connectivité effective. Des études

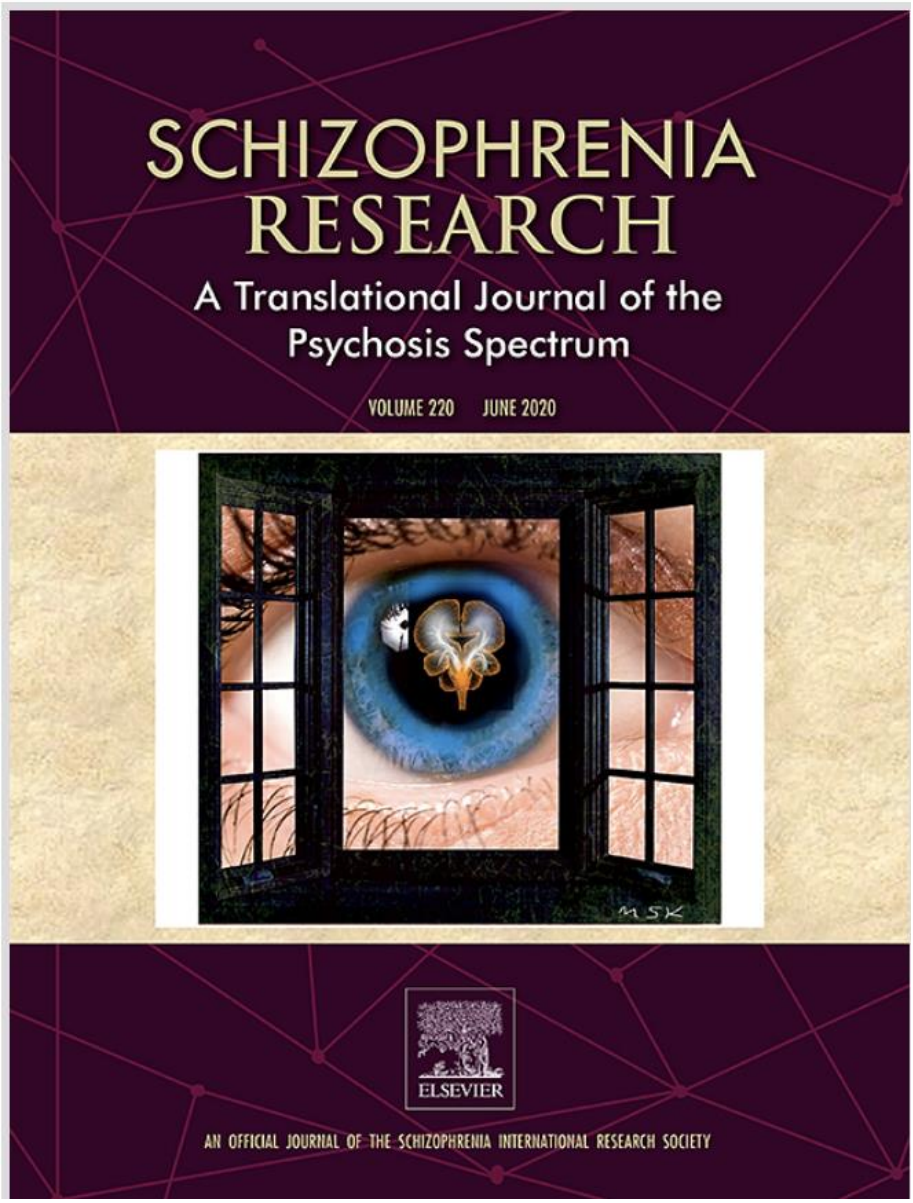
‘trait’ supplémentaires semblent nécessaires, afin de pouvoir réaliser ultérieurement des mesures dynamiques des expériences intrusives dans le TPST.

II. Anticipation de récompense et symptômes positifs dans la schizophrénie

La motivation est l'un des aspects majeurs de la saillance chez l'être humain. Notamment, des altérations de la motivation sont retrouvées dès les stades précoces de la schizophrénie (Foussias & Remington, 2010; Schlosser et al., 2014). Elles sont caractérisées par un déficit dans l'anticipation des récompenses futures, et ont été reliées à la fois aux symptômes positifs et négatifs du spectre schizophrénique. La dopamine joue un rôle central dans la physiopathologie de la schizophrénie (Diederen & Fletcher, 2020; Howes et al., 2015, 2020), mais elle est également fortement impliquée dans les signaux de récompense (Schultz, 2001). Dans ce contexte, le rôle exact que pourraient jouer les antagonistes des récepteurs dopaminergiques D2 (principaux traitements médicamenteux utilisés dans la schizophrénie) dans les altérations des signaux de récompense est encore débattu. Malgré plusieurs méta-analyses récentes (Chase et al., 2018; Radua et al., 2015), cette question reste étrangement à éclaircir. Par ailleurs, l'inclusion d'un nombre significatif d'études focalisées sur des régions d'intérêt dans ces méta-analyses, en particulier sur le striatum, constitue un risque non-négligeable de biais de sélection à même d'exclure des régions extérieures au striatum pouvant avoir un rôle dans ces processus. Enfin, le lien entre ces altérations et la sévérité des symptômes n'a pas encore été totalement exploré.

Afin de répondre à ces différentes questions, nous avons réalisé une nouvelle méta-analyse basée sur les coordonnées portant sur les études d'imagerie fonctionnelle comparant les signaux d'anticipation de récompense entre patients souffrant de schizophrénie et témoins sains (Leroy et al., 2020). Onze études de qualité méthodologique suffisante ont été incluses. Nous avons observé une réduction de la différence d'activation chez les patients avec schizophrénie au sein d'un réseau fronto-striatal. L'analyse par méta-régression a révélé que cette signature fonctionnelle était liée à la sévérité des symptômes psychotiques, et en particulier des symptômes positifs. Ces résultats ont persisté après contrôle de la dose de traitement antipsychotique (normalisée en équivalents Chlorpromazine, eqCPZ).

ARTICLE 1



Reward anticipation in schizophrenia: a coordinate-based meta-analysis

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Reward anticipation in schizophrenia: a coordinate-based meta-analysis

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DATA AVAILABILITY: the SDM map from this study will be made available on the NeuroVault repository (https://identifiers.org/neurovault.collection:6255)

AUTHOR CONTRIBUTION:

AL & RJ designed the study, collected the data and made the analyses. All the authors participated in the interpretation of results, the manuscript redaction and approved its final version.

ABSTRACT

Reward processing impairments have been linked with positive and negative symptoms of schizophrenia. Here, we performed a coordinate-based meta-analysis that combined eleven BOLD-fMRI studies comparing reward anticipation signals between schizophrenia patients and healthy controls. We observed a reduced difference in activation in schizophrenia patients within a frontal-striatal network. Meta-regressions revealed that this functional signature was linked to the severity of psychotic symptoms and persisted even after controlling for the dose of antipsychotic medications.

Key words: reward, salience, schizophrenia, antipsychotics, fMRI, meta-analysis.

INTRODUCTION

Motivation is considered to be one of the major aspects of salience in humans (Winton-Brown et al., 2014). Furthermore, motivational impairments are considered to be cardinal in schizophrenia and can be observed from the earliest stages of the disorder (Foussias and Remington, 2010; Schlosser et al., 2014). These impairments are related to deficits in anticipating future rewards (Juckel et al., 2006; Simon et al., 2010) and were shown to be associated with specific clinical features of schizophrenia. On the one hand, reward anticipation seems to be involved in the genesis of positive symptoms, i.e., hallucinations and delusions (Kapur, 2003; Murray et al., 2008), while suppressed reward processing could contribute to the reinforcement of negative symptoms, such as anhedonia (Barch and Dowd, 2010; Gold et al., 2008).

Dopamine plays a central role in the pathophysiology of schizophrenia (Howes et al., 2015), and it has also been implicated in reward signaling since dopamine neurons exhibit phasic firing during reward tasks in animals (Schultz, 2001). For several decades, D2 antagonists have been used as the reference pharmacological treatment for schizophrenia. However, their exact role in reward processing in this disorder, especially in reward anticipation, is still subject to debate (Juckel, 2016; Nielsen et al., 2018, 2012; Schlagenhauf et al., 2014).

Recent meta-analyses have addressed the question of the neural bases of reward signalling in schizophrenia and revealed activation changes in the ventral striatum (Chase et al., 2018; Radua et al., 2015). Despite the great interest these studies attract, some questions remain unanswered: (a) the inclusion of a significant number of region-of-interest (ROI) studies has exposed these meta-analyses to a bias towards the striatum. In this context, it remains difficult to fully exclude the possibility that some parts of the network involved in reward may have been missed; (b) the impact of symptom severity or medication on the resulting maps has not been directly explored.

To further these findings, we conducted a new coordinate-based meta-analysis of functional Magnetic Resonance Imaging (fMRI) studies comparing appetitive anticipation signals between patients with schizophrenia and healthy controls. Because salience and

reward are heterogeneous concepts, we chose to focus only on anticipation rather than on more learning-dependent signals (such as reward outcome or prediction error). The aim of this work was twofold: (i) determining the whole-brain bases of reward anticipation in schizophrenia; and (ii) clarifying the impact of potential moderators on the main findings (i.e. severity, antipsychotics dosage).

METHODS

Literature Selection, Data collection and preparation

We conducted systematic MEDLINE searches until September 2018 to identify task-based functional brain imaging studies on reward in schizophrenia. We used the following algorithm: ("schizophren* OR psychosis" "fMRI OR PET" "salienc* OR reward), complemented by the "related articles" function of the PubMed database and the reference list of studies found. To avoid bias towards the striatum, we only considered primary-data articles reporting whole-brain analyses or more than three ROIs. Among the 367 initial hits, eleven met our inclusion/exclusion criteria (see the PRISMA Flowchart in Figure S1). Selected activation studies are listed in Table 1 (Chung and Barch, 2016; da Silva Alves et al., 2013; Gradin et al., 2011; Koch et al., 2010; Potvin et al., 2016; Reckless et al., 2015; Richter et al., 2015; Schlagenhauf et al., 2009; Smieskova et al., 2015; Subramaniam et al., 2015; Walter et al., 2009). They referred to a Monetary Incentive Delay (MID) or similar task and reported the following fMRI contrasts: [reward anticipation vs. neutral cue] in [controls vs. schizophrenia patients]. Both controls > schizophrenia and schizophrenia > controls contrasts are reported, because the SDM meta-analysis software accounts for peaks' effect size and sign to counteract positive and negative differences. Stereotaxic coordinates of the 44 foci of interest for these contrasts were extracted and tagged by study and sample size. We considered only foci reported as significant at an uncorrected p-value < 0.001 or p-value < 0.05 corrected for multiple comparisons in the source studies.

Meta-Analysis Procedure

Data were analyzed using the SDM (seed-based d mapping) algorithm (Radua et al., 2012; Radua and Mataix-Cols, 2009). Effect sizes were calculated using (i) t-scores in the voxels containing a peak and (ii) a Gaussian kernel applied to the surrounding voxels (Radua et al., 2014). Estimated statistical maps were then included in a random effects meta-analytic model that weighted the contribution of each study according to its sample size and intra/interstudy heterogeneity. The statistical significance of the resulting SDM Z-maps was estimated through 50 permutation tests. Following standard criteria, intergroup comparisons were limited to (i) $p < 0.005$ (Rauch et al., 2002); (ii) an SDM Z-score >1; and (iii) a cluster extent >10 voxels (Radua et al., 2012; Radua and Mataix- Cols, 2009). A jackknife sensitivity analysis was conducted to assess the robustness of the findings by iteratively repeating the analysis and by excluding one dataset at a time, while a potential publication bias was assessed using Egger's tests and funnel plots. We verified that when results were changed in a particular dataset combination in the jackknife analysis, the discarded study did not drive the results using a visual inspection of funnel plots. We also verified that Egger's test was not significant ($p > 0.05$).

Finally, we performed voxelwise meta-regressions to assess the influence of potential moderators on the Group x Reward effect. For symptom severity, we used the average Positive and Negative Syndrome Scale (PANSS) total and subscores from each study. When necessary, a conversion from other scales to the PANSS was performed (van Erp et al., 2014). We also investigated the impact of the medication dosage converted to chlorpromazine equivalents (Gardner et al., 2010) on group differences. The moderating role of antipsychotics was then controlled for the mean symptom severity. Meta-regressions were limited to $p<0.0005$ (Thorsen et al., 2018), while findings in regions other than those detected in the main analyses were discarded (Radua and Mataix-Cols, 2009).

RESULTS

Meta-analytical estimates of brain responses during reward anticipation

We collected data for 488 subjects (254 schizophrenia patients and 234 controls) and 44 foci (**Table 1**). When comparing controls with patients for the [reward anticipation vs. neutral cue] contrast, we demonstrated an increased difference in activation, i.e., [reward anticipation > neutral cue] in [controls > schizophrenia patients], within a network involving the left striatum, the right median cingulate/paracingulate gyri, the left thalamus, the left postcentral gyrus, the left middle frontal gyrus, the cerebellum and the superior temporal gyrus.

After applying a jackknife analysis (testing for heterogeneity between clusters), Egger's tests and funnel plots (testing for the heterogeneity between studies), only the left striatum and the right median cingulate/paracingulate gyri remained reliable regions for consideration in the [controls>schizophrenia patients] contrast (Figure 1A). No significant difference was demonstrated for the [schizophrenia patients>controls] contrast (**Table S1**).

Table 1: Characteristics of the activation studies included in the meta-analysis. Mixed studies recruited patients corresponding to (a) *first-episode psychosis* and (b) *chronic schizophrenia* categories.

Study	Number of patients	Type of patients	Number of controls	Number of foci	Design
Alves et al.	10	First episode	12	2	Monetary incentive Delay Task
Gradin et al.	15	Chronic	20	5	Instrumental reward learning task
Koch et al.	44	Chronic	44	21	Monetary incentive Delay Task
Walter et al.	16	Chronic	16	1	Monetary incentive Delay Task
Schlagenhauf et al.	15	First episode and chronic	15	2	Monetary incentive Delay Task
Smieskova et al.	29	First episode	19	3	Salience Attribution Task
Subramaniam et al.	37	Chronic	20	1	Monetary incentive Delay Task
Richter et al.	16	Chronic	16	5	Desire-reason-dilemma paradigm
Chung et al.	36	Chronic	27	1	Variant of a response conflict task
Potvin et al.	18	Chronic	24	2	Cue associated with smoking
Reckless et al	18	Chronic	21	1	Rewarded perceptual decision-making task

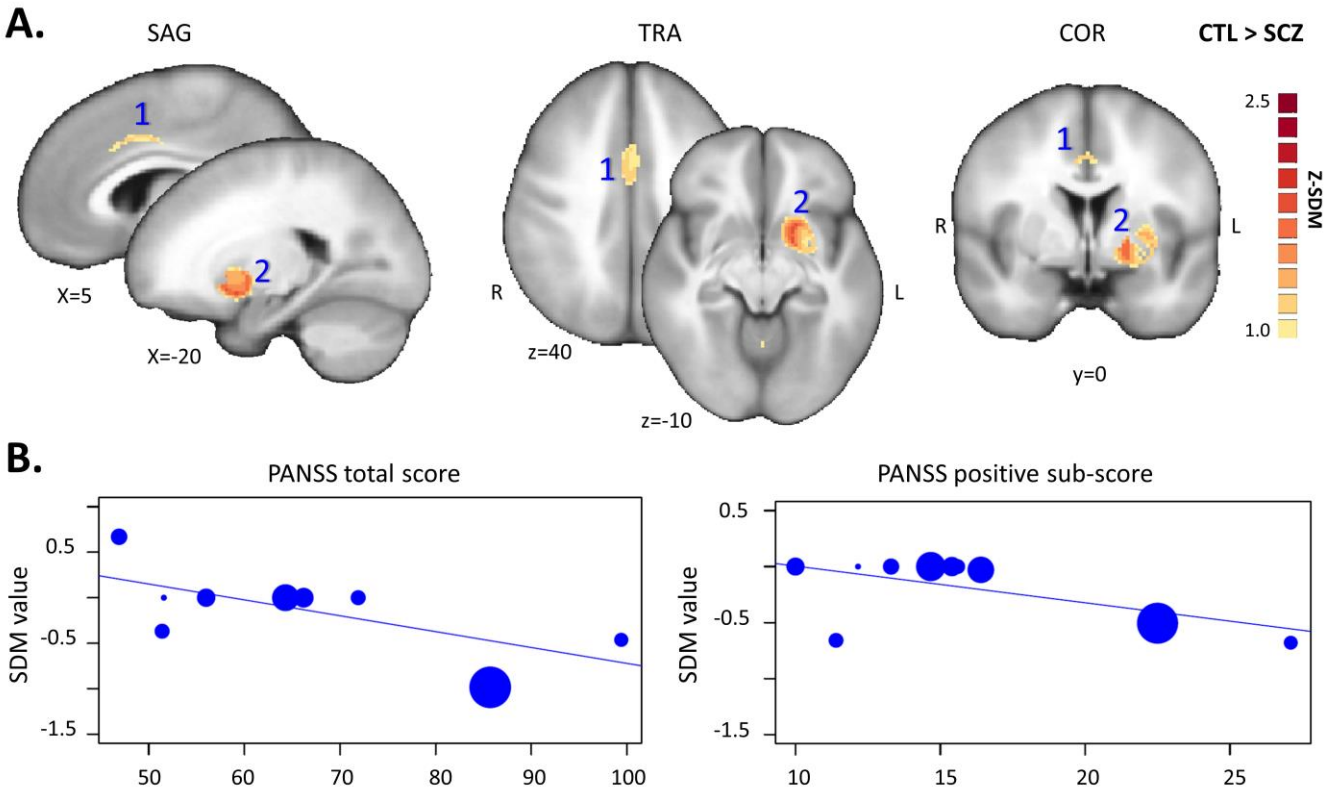


Figure 1: Coordinate-based meta-analytic findings for reward anticipation in schizophrenia.

1A. Inter-group effect size on signed differential maps during reward anticipation in schizophrenia. The right median cingulate/paracingulate gyri (**1**) and left striatum (**2**) were significant for the contrast [controls > schizophrenia patients (SCZ)] and survived (a) jackknife analysis, (b) Egger's tests and (c) funnel plots analyses.

1B. Meta-regression analysis testing for an association between symptom severity in the left striatum. Larger circles indicate studies with a larger sample size. The meta-regression SDM slope after controlling for the dosage of antipsychotics is presented as a straight line for average PANSS global scores (left panel) and PANSS positive sub-scores (right panel). Note that the meta-regression SDM value is derived from the proportion of studies that reported BOLD change near the voxel, so it is expected that the values of some of the studies are at 0 or near +1 (instead of being close to the line). "PANSS": Positive and Negative Syndrome Scale; "SDM": signed d mapping.

Potential effect of symptoms severity and medication

Voxel-wise meta-regressions revealed that the left striatum was more affected in the contrast [reward anticipation > neutral cue] in [controls > schizophrenia patients] in severe schizophrenia patients (i.e. with higher total PANSS scores), independent of medication (**Figure 1B**). More precisely, less striatal activation was demonstrated in patients exhibiting more severe psychotic symptoms (PANSS positive sub-scores), even after controlling for the dosage of antipsychotics (**Figure 1B**).

DISCUSSION

In the present paper, we produced robust whole-brain meta-analytic maps associated with reward anticipation in schizophrenia. We showed that during reward anticipation, schizophrenia patients exhibit a reduced difference in activation in two key nodes of the putative salience network, the left striatum and the cingulate/paracingulate gyri. These findings support the idea that reward anticipation extends beyond the ventral striatum (VS) (Radua et al., 2015). Furthermore, our results are fully compatible with recent exploration in the healthy brain underscoring the role played by these nodes in reward anticipation (Wilson et al., 2018). Critically, we showed that within this salience network, VS hypoactivation was more pronounced in schizophrenia patients exhibiting more severe positive symptoms. These results remained significant even after controlling for the effect of antipsychotic dosage, suggesting that they are not driven by medication (Juckel, 2016).

Despite some methodological differences, our findings nicely complement three previous meta-analyses addressing similar questions: one taking a strict region-of-interest approach (Radua et al., 2015); another using a transdiagnosis approach, beyond schizophrenia (Zhang et al., 2016); and a last one that explored wider and more heterogeneous reward-related brain activation (Chase et al., 2018). We made the choice to focus only on anticipation of reward studies to favor a homogeneous selection of activation studies. Even if this remains a point of debate, some studies have suggested that anticipation of reward and prediction error may only partially share their neural bases. First, at the behavioral level (as in MID tasks), processes related to anticipation, outcome and prediction error can be separated (Knutson et al., 2000). Furthermore, electrophysiological studies have reported that reward signals of dopamine neurons were influenced by reward predictability (Hollerman and Schultz, 1998). Finally, recent fMRI studies (Cao et al., 2019) have shown that different reward processing stages during the MID task were associated with distinct patterns of activation and connectivity. By performing a new prediction-error meta-analysis (based on 11 studies and using similar selection quality criteria), we were also able to provide evidence for differences with anticipation of reward, notably a nonrobust significant result in the cingulate for the [controls>schizophrenia patients] contrast (**Table S2**). What can initially appear as a power issue (i.e., 11 selected studies) was in fact balanced

by the quality and homogeneity of the papers used (Müller et al., 2018). We further ensured the robustness of our findings by (i) taking into account covariates such as symptom severity and medications, (ii) applying a restrictive threshold (Thorsen et al., 2018), and (iii) conducting a sensitivity analysis. However, the small number of studies makes it impossible to examine other issues, such as whether the results differed as a function of paradigms (e.g., MID vs. other types of tasks) or stages of illness (early vs chronic).

Furthermore, emotionally salient stimuli could have been an issue in the generation of reproducible findings because of their greater dependence on the patient's history (Winton-Brown et al., 2014), and we excluded studies using these kinds of stimuli. In contrast, reward stimuli, such as monetary rewards, seem more reliable (Daniel and Pollmann, 2010). The brain responses were also shown to vary between different types of salience, such as emotional salience or salience linked to novelty (Knolle et al., 2018). At this stage, it remains difficult to fully exclude the possibility that alternative procedures may have resulted in different reward-related functional results in the VS and, more globally, in the salience network. For instance, we did not replicate left VS hypoactivation in patients with more negative symptoms, which was a result observed in a previous striatum-focused meta-analysis (Radua et al., 2015).

Overall, we demonstrated a robust frontal-striatal signature of impaired reward anticipation in schizophrenia patients. In this study, we aimed to analyze a very homogeneous selection of studies, to reflect on paper selection from the reward literature and to perform meta-regression on symptom severity and dosage of treatment, which has not been done before. Within this functional network, VS hypoactivation was linked to the severity of psychotic symptoms, even when controlling for medication dosage.

SUPPLEMENTARY MATERIAL

Table S1. Coordinate-based meta-analytic complementary results. Brain regions with significant activations during reward anticipation for the contrast [controls > patients with schizophrenia] or [patients with schizophrenia > controls]. MNI: Montreal Neurological Institute; "*" means nearest grey matter.

Clusters	Coordinate (MNI)	Number of voxels	p	SDM-Z	Label	Jacknife	p Egger's test
1	-16,6,-4	606	0.000045538	-2.137	Left striatum	9/11	0.553
2	6,8,36	110	0.001922309	-1.635	Right median cingulate/paracingulate gyri	9/11	0.268
3	-2,-14,6	80	0.001346052	-1.691	Left thalamus	10/11	0.016
4	-42,-16,34	35	0.001594365	-1.666	Left postcentral gyrus*	10/11	0.063
5	-38,50,0	24	0.002998114	-1.56	Left middle frontal gyrus	1/11	0.028
6	4,-60,-8	22	0.003202200	-1.548	Cerebellum, vermic lobule, BA 18	10/11	0.054
7	56,12,-12	11	0.002559066	-1.587	Right temporal pole, superior temporal gyrus, BA 38	9/11	0.023

Table S2. Coordinate-based meta-analytic complementary results. Brain regions with significant activations during prediction error for the contrast [controls > patients with schizophrenia] or [patients with schizophrenia > controls]. MNI: Montreal Neurological Institute; "*" means nearest grey matter.

Clusters	Coordinate (MNI)	Number of voxels	p	SDM-Z	Label	Jacknife	p Egger's test
1	0, -42, 36	659	0,000508249	-1,82	Left median cingulate/paracingulate gyri	6/10	0.09
2	0, -6, -8	148	0,000837684	-1,754	undefined	2/10	0.20
3	-2,-14,6	36	0,003093004	-1,556	Right precuneus	7/10	0.14

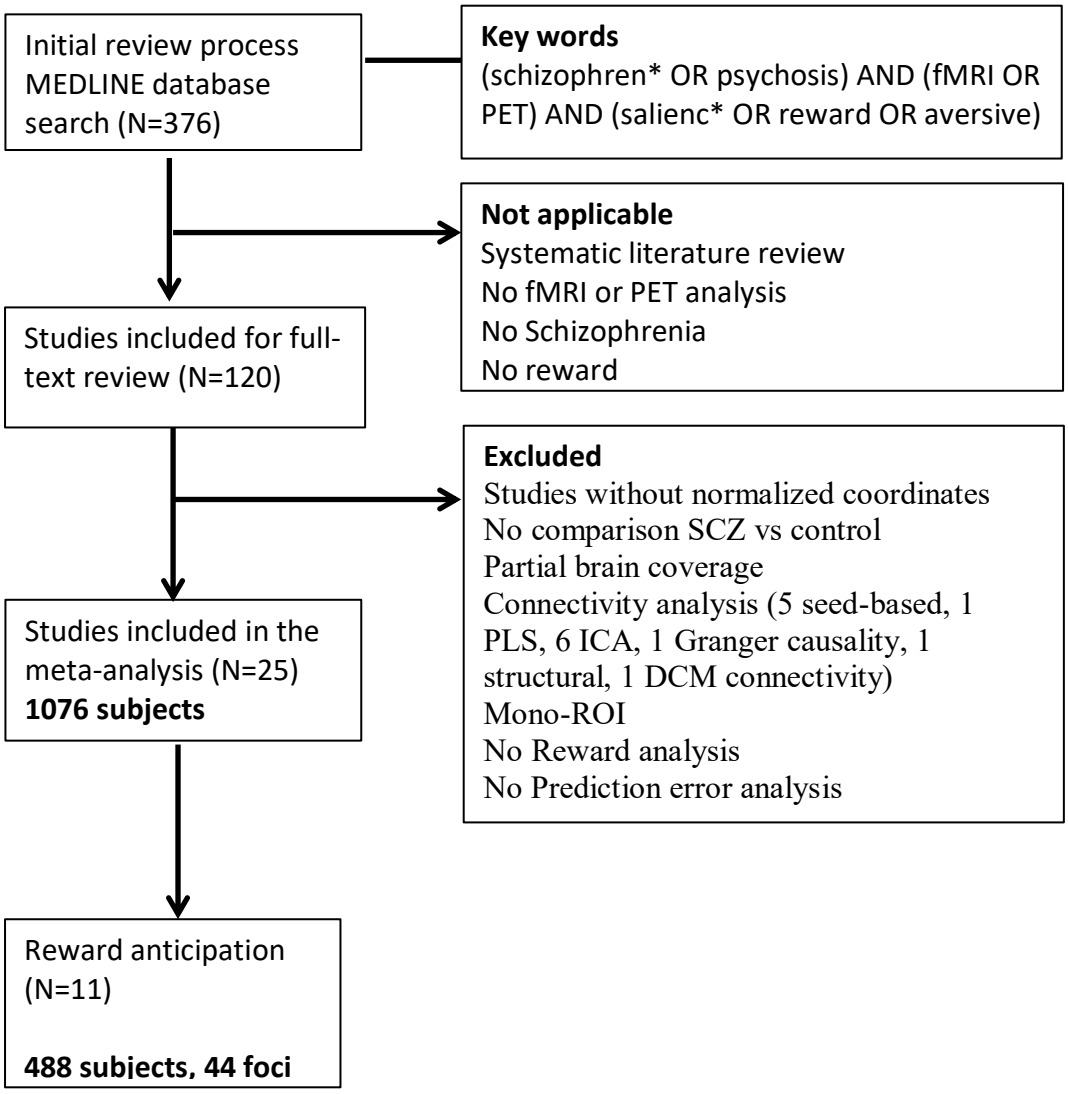


Figure S1. PRISMA Flow diagram of article selection process.

REFERENCES

Barch, D.M., Dowd, E.C., 2010. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr. Bull. 36, 919–934. https://doi.org/10.1093/schbul/sbq068

Chase, H.W., Loriemi, P., Wensing, T., Eickhoff, S.B., Nickl-Jockschat, T., 2018. Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia. Hum. Brain Mapp. 39, 2917–2928. https://doi.org/10.1002/hbm.24049

Chung, Y.S., Barch, D.M., 2016. Frontal-striatum dysfunction during reward processing: Relationships to amotivation in schizophrenia. J. Abnorm. Psychol. 125, 453–469. https://doi.org/10.1037/abn0000137

da Silva Alves, F., Bakker, G., Schmitz, N., Abeling, N., Hasler, G., van der Meer, J., Nederveen, A., de Haan, L., Linszen, D., van Amelsvoort, T., 2013. Dopaminergic modulation of the reward system in schizophrenia: a placebo-controlled dopamine depletion fMRI study. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 23, 1577–1586. https://doi.org/10.1016/j.euroneuro.2013.06.008

Foussias, G., Remington, G., 2010. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr. Bull. 36, 359–369. https://doi.org/10.1093/schbul/sbn094

Gold, J.M., Waltz, J.A., Prentice, K.J., Morris, S.E., Heerey, E.A., 2008. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr. Bull. 34, 835–847. https://doi.org/10.1093/schbul/sbn068

Gradin, V.B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., Reid, I., Hall, J., Steele, J.D., 2011. Expected value and prediction error abnormalities in depression and schizophrenia. Brain J. Neurol. 134, 1751–1764. https://doi.org/10.1093/brain/awr059

Hollerman, J.R., Schultz, W., 1998. Dopamine neurons report an error in the temporal prediction of reward during learning. Nat. Neurosci. 1, 304–309. https://doi.org/10.1038/1124

Howes, O., McCutcheon, R., Stone, J., 2015. Glutamate and dopamine in schizophrenia: an update for the 21st century. J. Psychopharmacol. Oxf. Engl. 29, 97–115. https://doi.org/10.1177/0269881114563634

Juckel, G., 2016. Inhibition of the reward system by antipsychotic treatment. Dialogues Clin. Neurosci. 18, 109–114.

Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. NeuroImage 29, 409–416. https://doi.org/10.1016/j.neuroimage.2005.07.051

Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am. J. Psychiatry 160, 13–23. https://doi.org/10.1176/appi.ajp.160.1.13

Knolle, F., Ermakova, A.O., Justicia, A., Fletcher, P.C., Bunzeck, N., Düzel, E., Murray, G.K., 2018. Brain responses to different types of salience in antipsychotic naïve first episode psychosis: An fMRI study. Transl. Psychiatry 8, 196. https://doi.org/10.1038/s41398-018-0250-3

Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. NeuroImage 12, 20–27. https://doi.org/10.1006/nimg.2000.0593

Koch, K., Schachtzabel, C., Wagner, G., Schikora, J., Schultz, C., Reichenbach, J.R., Sauer, H.,

Schlösser, R.G.M., 2010. Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. NeuroImage 50, 223–232. https://doi.org/10.1016/j.neuroimage.2009.12.031
Müller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Radua, J., Mataix-Cols, D., Tench, C.R., Yarkoni, T., Nichols, T.E., Turkeltaub, P.E., Wager, T.D., Eickhoff, S.B., 2018. Ten simple rules for neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 84, 151–161. https://doi.org/10.1016/j.neubiorev.2017.11.012
Murray, G., Corlett, P., Clark, L., Pessiglione, M., Blackwell, A., Honey, G., Jones, P., Bullmore, E., Robbins, T., Fletcher, P., 2008. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol. Psychiatry 13, 239–276. https://doi.org/10.1038/sj.mp.4002058
Nielsen, M.Ø., Rostrup, E., Broberg, B.V., Wulff, S., Glenthøj, B., 2018. Negative Symptoms and Reward Disturbances in Schizophrenia Before and After Antipsychotic Monotherapy. Clin. EEG Neurosci. 49, 36–45. https://doi.org/10.1177/1550059417744120
Nielsen, M.O., Rostrup, E., Wulff, S., Bak, N., Broberg, B.V., Lublin, H., Kapur, S., Glenthoj, B., 2012. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch. Gen. Psychiatry 69, 1195–1204. https://doi.org/10.1001/archgenpsychiatry.2012.847
Potvin, S., Lungu, O., Lipp, O., Lalonde, P., Zaharieva, V., Stip, E., Melun, J.-P., Mendrek, A., 2016. Increased ventro-medial prefrontal activations in schizophrenia smokers during cigarette cravings. Schizophr. Res. 173, 30–36. https://doi.org/10.1016/j.schres.2016.03.011
Radua, J., Grau, M., van den Heuvel, O.A., Thiebaut de Schotten, M., Stein, D.J., Canales-Rodríguez, E.J., Catani, M., Mataix-Cols, D., 2014. Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 39, 1547–1557. https://doi.org/10.1038/npp.2014.5
Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br. J. Psychiatry J. Ment. Sci. 195, 393–402. https://doi.org/10.1192/bjp.bp.108.055046
Radua, J., Mataix-Cols, D., Phillips, M.L., El-Hage, W., Kronhaus, D.M., Cardoner, N., Surguladze, S., 2012. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur. Psychiatry J. Assoc. Eur. Psychiatr. 27, 605–611. https://doi.org/10.1016/j.eurpsy.2011.04.001
Radua, J., Schmidt, A., Borgwardt, S., Heinz, A., Schlagenhauf, F., McGuire, P., Fusar-Poli, P., 2015. Ventral Striatal Activation During Reward Processing in Psychosis: A Neurofunctional Meta-Analysis. JAMA Psychiatry 72, 1243–1251. https://doi.org/10.1001/jamapsychiatry.2015.2196
Rauch, S.L., Shin, L.M., Dougherty, D.D., Alpert, N.M., Fischman, A.J., Jenike, M.A., 2002. Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 27, 782–791. https://doi.org/10.1016/S0893-133X(02)00351-2
Reckless, G.E., Andreassen, O.A., Server, A., Østefjells, T., Jensen, J., 2015. Negative symptoms in schizophrenia are associated with aberrant striato-cortical connectivity in a rewarded perceptual decision-making task. NeuroImage Clin. 8, 290–297. https://doi.org/10.1016/j.nicl.2015.04.025
Richter, A., Petrovic, A., Diekhof, E.K., Trost, S., Wolter, S., Gruber, O., 2015. Hyperresponsivity and impaired prefrontal control of the mesolimbic reward system in schizophrenia. J. Psychiatr. Res. 71, 8–15. https://doi.org/10.1016/j.jpsychires.2015.09.005

Schlagenhauf, F., Huys, Q.J.M., Deserno, L., Rapp, M.A., Beck, A., Heinze, H.-J., Dolan, R., Heinz, A., 2014. Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. NeuroImage 89, 171–180. https://doi.org/10.1016/j.neuroimage.2013.11.034
Schlagenhauf, F., Sterzer, P., Schmack, K., Ballmaier, M., Rapp, M., Wrase, J., Juckel, G., Gallinat, J., Heinz, A., 2009. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. Biol. Psychiatry 65, 1032–1039. https://doi.org/10.1016/j.biopsych.2008.12.016
Schlosser, D.A., Fisher, M., Gard, D., Fulford, D., Loewy, R.L., Vinogradov, S., 2014. Motivational deficits in individuals at-risk for psychosis and across the course of schizophrenia. Schizophr. Res. 158, 52–57. https://doi.org/10.1016/j.schres.2014.06.024
Schultz, W., 2001. Reward signaling by dopamine neurons. Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry 7, 293–302. https://doi.org/10.1177/107385840100700406
Simon, J.J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., Kaiser, S., 2010. Neural correlates of reward processing in schizophrenia--relationship to apathy and depression. Schizophr. Res. 118, 154–161. https://doi.org/10.1016/j.schres.2009.11.007
Smieskova, R., Roiser, J.P., Chaddock, C.A., Schmidt, A., Harrisberger, F., Bendfeldt, K., Simon, A., Walter, A., Fusar-Poli, P., McGuire, P.K., Lang, U.E., Riecher-Rössler, A., Borgwardt, S., 2015. Modulation of motivational salience processing during the early stages of psychosis. Schizophr. Res. 166, 17–23. https://doi.org/10.1016/j.schres.2015.04.036
Subramaniam, K., Hooker, C.I., Biagianti, B., Fisher, M., Nagarajan, S., Vinogradov, S., 2015. Neural signal during immediate reward anticipation in schizophrenia: Relationship to real-world motivation and function. NeuroImage Clin. 9, 153–163. https://doi.org/10.1016/j.nicl.2015.08.001
Thorsen, A.L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., van den Heuvel, O.A., 2018. Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 563–571. https://doi.org/10.1016/j.bpsc.2018.01.009
van Erp, T.G.M., Preda, A., Nguyen, D., Faziola, L., Turner, J., Bustillo, J., Belger, A., Lim, K.O., McEwen, S., Voyvodic, J., Mathalon, D.H., Ford, J., Potkin, S.G., Fbirn, null, 2014. Converting positive and negative symptom scores between PANSS and SAPS/SANS. Schizophr. Res. 152, 289–294. https://doi.org/10.1016/j.schres.2013.11.013
Walter, H., Kammerer, H., Frasch, K., Spitzer, M., Abler, B., 2009. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology (Berl.) 206, 121–132. https://doi.org/10.1007/s00213-009-1586-4
Wilson, R.P., Colizzi, M., Bossong, M.G., Allen, P., Kempton, M., MTAC, Bhattacharyya, S., 2018. The Neural Substrate of Reward Anticipation in Health: A Meta-Analysis of fMRI Findings in the Monetary Incentive Delay Task. Neuropsychol. Rev. https://doi.org/10.1007/s11065-018-9385-5
Winton-Brown, T.T., Fusar-Poli, P., Ungless, M.A., Howes, O.D., 2014. Dopaminergic basis of salience dysregulation in psychosis. Trends Neurosci. 37, 85–94. https://doi.org/10.1016/j.tins.2013.11.003
Zhang, B., Lin, P., Shi, H., Öngür, D., Auerbach, R.P., Wang, Xiaosheng, Yao, S., Wang, Xiang, 2016. Mapping anhedonia-specific dysfunction in a transdiagnostic approach: an ALE meta-analysis. Brain Imaging Behav. 10, 920–939. https://doi.org/10.1007/s11682-015-9457-6
Barch, D.M., Dowd, E.C., 2010. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr. Bull. 36, 919–934.

https://doi.org/10.1093/schbul/sbq068
Chase, H.W., Loriemi, P., Wensing, T., Eickhoff, S.B., Nickl-Jockschat, T., 2018. Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia. Hum. Brain Mapp. 39, 2917–2928. https://doi.org/10.1002/hbm.24049
Chung, Y.S., Barch, D.M., 2016. Frontal-striatum dysfunction during reward processing: Relationships to amotivation in schizophrenia. J. Abnorm. Psychol. 125, 453–469. https://doi.org/10.1037/abn0000137
da Silva Alves, F., Bakker, G., Schmitz, N., Abeling, N., Hasler, G., van der Meer, J., Nederveen, A., de Haan, L., Linszen, D., van Amelsvoort, T., 2013. Dopaminergic modulation of the reward system in schizophrenia: a placebo-controlled dopamine depletion fMRI study. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 23, 1577–1586. https://doi.org/10.1016/j.euroneuro.2013.06.008
Foussias, G., Remington, G., 2010. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr. Bull. 36, 359–369. https://doi.org/10.1093/schbul/sbn094
Gold, J.M., Waltz, J.A., Prentice, K.J., Morris, S.E., Heerey, E.A., 2008. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr. Bull. 34, 835–847. https://doi.org/10.1093/schbul/sbn068
Gradin, V.B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., Reid, I., Hall, J., Steele, J.D., 2011. Expected value and prediction error abnormalities in depression and schizophrenia. Brain J. Neurol. 134, 1751–1764. https://doi.org/10.1093/brain/awr059
Hollerman, J.R., Schultz, W., 1998. Dopamine neurons report an error in the temporal prediction of reward during learning. Nat. Neurosci. 1, 304–309. https://doi.org/10.1038/1124
Howes, O., McCutcheon, R., Stone, J., 2015. Glutamate and dopamine in schizophrenia: an update for the 21st century. J. Psychopharmacol. Oxf. Engl. 29, 97–115. https://doi.org/10.1177/0269881114563634
Juckel, G., 2016. Inhibition of the reward system by antipsychotic treatment. Dialogues Clin. Neurosci. 18, 109–114.
Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. NeuroImage 29, 409–416. https://doi.org/10.1016/j.neuroimage.2005.07.051
Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am. J. Psychiatry 160, 13–23. https://doi.org/10.1176/appi.ajp.160.1.13
Knolle, F., Ermakova, A.O., Justicia, A., Fletcher, P.C., Bunzeck, N., Düzel, E., Murray, G.K., 2018. Brain responses to different types of salience in antipsychotic naïve first episode psychosis: An fMRI study. Transl. Psychiatry 8, 196. https://doi.org/10.1038/s41398-018-0250-3
Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. NeuroImage 12, 20–27. https://doi.org/10.1006/nimg.2000.0593
Koch, K., Schachtzabel, C., Wagner, G., Schikora, J., Schultz, C., Reichenbach, J.R., Sauer, H., Schlösser, R.G.M., 2010. Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. NeuroImage 50, 223–232. https://doi.org/10.1016/j.neuroimage.2009.12.031
Müller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Radua, J., Mataix-Cols, D., Tench, C.R., Yarkoni, T., Nichols, T.E., Turkeltaub, P.E., Wager, T.D., Eickhoff, S.B., 2018. Ten simple rules for

neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 84, 151–161. https://doi.org/10.1016/j.neubiorev.2017.11.012
Murray, G., Corlett, P., Clark, L., Pessiglione, M., Blackwell, A., Honey, G., Jones, P., Bullmore, E., Robbins, T., Fletcher, P., 2008. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol. Psychiatry 13, 239–276. https://doi.org/10.1038/sj.mp.4002058
Nielsen, M.Ø., Rostrup, E., Broberg, B.V., Wulff, S., Glenthøj, B., 2018. Negative Symptoms and Reward Disturbances in Schizophrenia Before and After Antipsychotic Monotherapy. Clin. EEG Neurosci. 49, 36–45. https://doi.org/10.1177/1550059417744120
Nielsen, M.O., Rostrup, E., Wulff, S., Bak, N., Broberg, B.V., Lublin, H., Kapur, S., Glenthoj, B., 2012. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch. Gen. Psychiatry 69, 1195–1204. https://doi.org/10.1001/archgenpsychiatry.2012.847
Potvin, S., Lungu, O., Lipp, O., Lalonde, P., Zaharieva, V., Stip, E., Melun, J.-P., Mendrek, A., 2016. Increased ventro-medial prefrontal activations in schizophrenia smokers during cigarette cravings. Schizophr. Res. 173, 30–36. https://doi.org/10.1016/j.schres.2016.03.011
Radua, J., Grau, M., van den Heuvel, O.A., Thiebaut de Schotten, M., Stein, D.J., Canales-Rodríguez, E.J., Catani, M., Mataix-Cols, D., 2014. Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 39, 1547–1557. https://doi.org/10.1038/npp.2014.5
Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br. J. Psychiatry J. Ment. Sci. 195, 393–402. https://doi.org/10.1192/bjp.bp.108.055046
Radua, J., Mataix-Cols, D., Phillips, M.L., El-Hage, W., Kronhaus, D.M., Cardoner, N., Surguladze, S., 2012. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur. Psychiatry J. Assoc. Eur. Psychiatr. 27, 605–611. https://doi.org/10.1016/j.eurpsy.2011.04.001
Radua, J., Schmidt, A., Borgwardt, S., Heinz, A., Schlagenhauf, F., McGuire, P., Fusar-Poli, P., 2015. Ventral Striatal Activation During Reward Processing in Psychosis: A Neurofunctional Meta-Analysis. JAMA Psychiatry 72, 1243–1251. https://doi.org/10.1001/jamapsychiatry.2015.2196
Rauch, S.L., Shin, L.M., Dougherty, D.D., Alpert, N.M., Fischman, A.J., Jenike, M.A., 2002. Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 27, 782–791. https://doi.org/10.1016/S0893-133X(02)00351-2
Reckless, G.E., Andreassen, O.A., Server, A., Østefjells, T., Jensen, J., 2015. Negative symptoms in schizophrenia are associated with aberrant striato-cortical connectivity in a rewarded perceptual decision-making task. NeuroImage Clin. 8, 290–297. https://doi.org/10.1016/j.nicl.2015.04.025
Richter, A., Petrovic, A., Diekhof, E.K., Trost, S., Wolter, S., Gruber, O., 2015. Hyperresponsivity and impaired prefrontal control of the mesolimbic reward system in schizophrenia. J. Psychiatr. Res. 71, 8–15. https://doi.org/10.1016/j.jpsychires.2015.09.005
Schlagenhauf, F., Huys, Q.J.M., Deserno, L., Rapp, M.A., Beck, A., Heinze, H.-J., Dolan, R., Heinz, A., 2014. Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. NeuroImage 89, 171–180. https://doi.org/10.1016/j.neuroimage.2013.11.034
Schlagenhauf, F., Sterzer, P., Schmack, K., Ballmaier, M., Rapp, M., Wrase, J., Juckel, G., Gallinat, J., Heinz, A., 2009. Reward feedback alterations in unmedicated schizophrenia

patients: relevance for delusions. Biol. Psychiatry 65, 1032–1039. https://doi.org/10.1016/j.biopsych.2008.12.016
Schlosser, D.A., Fisher, M., Gard, D., Fulford, D., Loewy, R.L., Vinogradov, S., 2014. Motivational deficits in individuals at-risk for psychosis and across the course of schizophrenia. Schizophr. Res. 158, 52–57. https://doi.org/10.1016/j.schres.2014.06.024
Schultz, W., 2001. Reward signaling by dopamine neurons. Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry 7, 293–302. https://doi.org/10.1177/107385840100700406
Simon, J.J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., Kaiser, S., 2010. Neural correlates of reward processing in schizophrenia--relationship to apathy and depression. Schizophr. Res. 118, 154–161. https://doi.org/10.1016/j.schres.2009.11.007
Smieskova, R., Roiser, J.P., Chaddock, C.A., Schmidt, A., Harrisberger, F., Bendfeldt, K., Simon, A., Walter, A., Fusar-Poli, P., McGuire, P.K., Lang, U.E., Riecher-Rössler, A., Borgwardt, S., 2015. Modulation of motivational salience processing during the early stages of psychosis. Schizophr. Res. 166, 17–23. https://doi.org/10.1016/j.schres.2015.04.036
Subramaniam, K., Hooker, C.I., Biagianti, B., Fisher, M., Nagarajan, S., Vinogradov, S., 2015. Neural signal during immediate reward anticipation in schizophrenia: Relationship to real-world motivation and function. NeuroImage Clin. 9, 153–163. https://doi.org/10.1016/j.nicl.2015.08.001
Thorsen, A.L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., van den Heuvel, O.A., 2018. Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 563–571. https://doi.org/10.1016/j.bpsc.2018.01.009
van Erp, T.G.M., Preda, A., Nguyen, D., Faziola, L., Turner, J., Bustillo, J., Belger, A., Lim, K.O., McEwen, S., Voyvodic, J., Mathalon, D.H., Ford, J., Potkin, S.G., Fbirn, null, 2014. Converting positive and negative symptom scores between PANSS and SAPS/SANS. Schizophr. Res. 152, 289–294. https://doi.org/10.1016/j.schres.2013.11.013
Walter, H., Kammerer, H., Frasch, K., Spitzer, M., Abler, B., 2009. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology (Berl.) 206, 121–132. https://doi.org/10.1007/s00213-009-1586-4
Wilson, R.P., Colizzi, M., Bossong, M.G., Allen, P., Kempton, M., MTAC, Bhattacharyya, S., 2018. The Neural Substrate of Reward Anticipation in Health: A Meta-Analysis of fMRI Findings in the Monetary Incentive Delay Task. Neuropsychol. Rev. https://doi.org/10.1007/s11065-018-9385-5
Winton-Brown, T.T., Fusar-Poli, P., Ungless, M.A., Howes, O.D., 2014. Dopaminergic basis of salience dysregulation in psychosis. Trends Neurosci. 37, 85–94. https://doi.org/10.1016/j.tins.2013.11.003
Zhang, B., Lin, P., Shi, H., Öngür, D., Auerbach, R.P., Wang, Xiaosheng, Yao, S., Wang, Xiang, 2016. Mapping anhedonia-specific dysfunction in a transdiagnostic approach: an ALE meta-analysis. Brain Imaging Behav. 10, 920–939. https://doi.org/10.1007/s11682-015-9457-6

III. Validation et réplication d'une méthode de capture hallucinatoire en imagerie par résonnance magnétique fonctionnelle (IRMf)

Cette seconde étude a permis de valider une méthode de capture hallucinatoire dite « en deux étapes », basée sur une analyse multivariée guidée par les données au cours d'un enregistrement IRMf per-hallucinatoire au repos (c'est-à-dire sans tâche pour le sujet), et ensuite complétée d'un questionnaire post-IRMf immédiat. Une *Analyse en Composante Indépendante* était réalisée sur le signal fonctionnel. La méthode du fingerprint était ensuite utilisée afin de sélectionner les composantes indépendantes d'intérêts (i.e., de source neurophysiologique), et par là-même de supprimer les composantes artéfactuelles. Les composantes retenues étaient ensuite comparées au questionnaire post-IRMf immédiat, et aux réseaux physiologiques d'intérêt (e.g., langage dans les hallucinations acoustico-verbales, etc.). Nous avons ainsi pu recueillir plusieurs éléments en faveur de la validité et la robustesse de cette méthode : (i) des performances élevées pour rapporter un stimuli sensoriel dans un contexte d'IRM, malgré la présence de symptômes psychotiques ou cognitifs chez les sujets en environnement contrôlé ; (ii) une bonne concordance de détection entre les méthodes basées sur les hypothèses et notre approche basée sur les données lorsque des stimuli sensoriels contrôlés sont présentés ; (iii) une bonne concordance entre la méthode en deux étapes et une approche basées sur la pression d'un bouton lors de la survenue d'un évènement hallucinatoire (considérée comme la méthodologie de référence) ; (iv) une forte consistance spatiale des réseaux impliqués dans

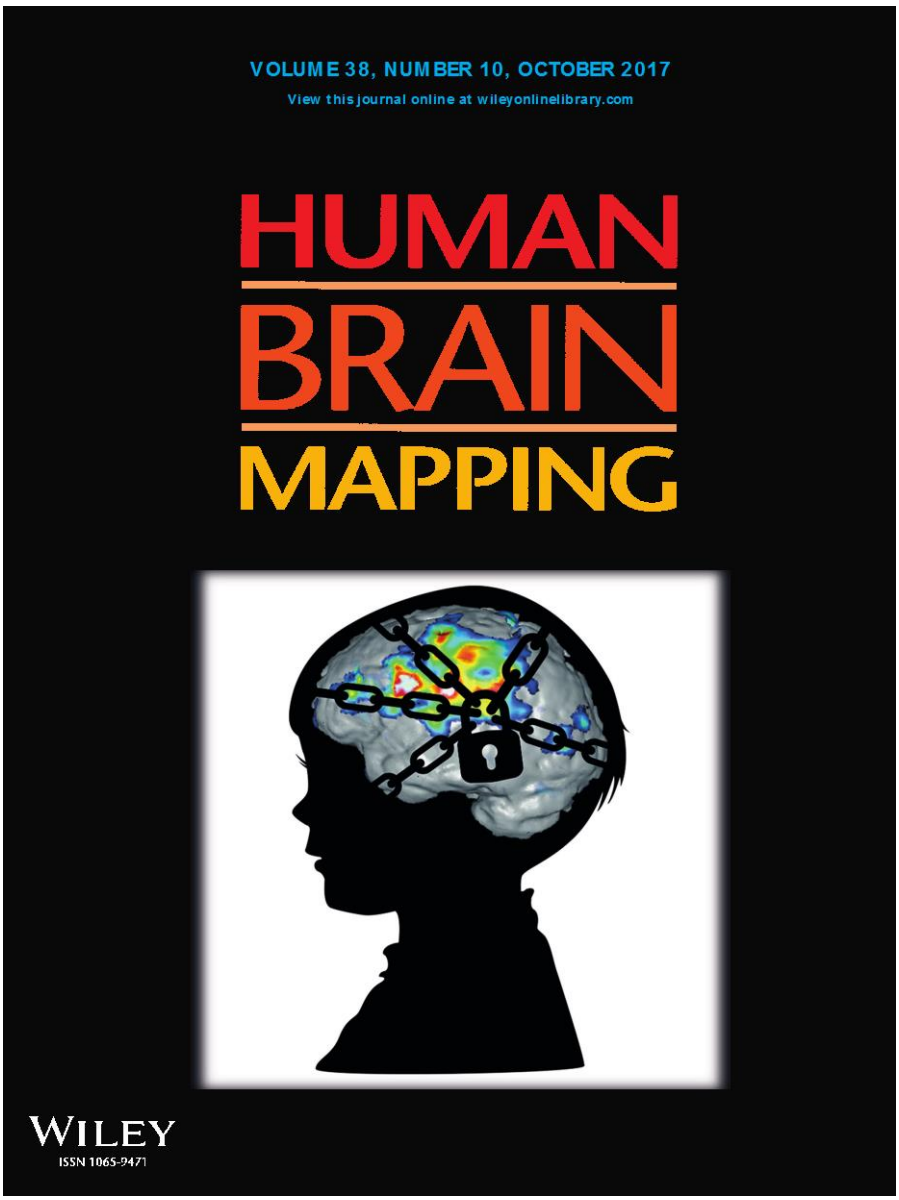
les hallucinations en utilisant la méthode en deux étapes au sein de deux échantillons indépendants.

Ces réseaux sont intimement liés aux réseaux de repos. En effet, dans cet article, nous avons également pu répliquer les résultats que nous avions déjà montrés sur un autre échantillon (Jardri et al., 2013), et qui montrent une anti-corrélation entre le signal des réseaux impliqués dans les expériences hallucinatoires et celui du DMN. De même, l'implication du SN, et en particulier de l'insula antérieure, est importante dans la survenue des expériences hallucinatoires. Elle a été retrouvée activée dans les études 'trait' s'intéressant aux bases neurales des hallucinations comme le montrent les méta-analyses d'IRMf (Jardri et al., 2011). Aussi, cette région est très connectée aux régions retrouvées lors de la capture hallucinatoire, notamment avec l'aire de Broca, qui est impliquée dans la production du langage.

Cette méthode nous a enfin permis dans une autre étude d'étudier la dynamique des réseaux de repos au cours des expériences hallucinatoires, et notamment le rôle du SN (Lefebvre et al., 2016). En effet, alors que le modèle du « réseau tripartite » (Menon & Uddin, 2010) qui inclut le DMN, le CEN et la SN, a déjà été étudié dans la schizophrénie, la façon dont ces trois réseaux interagissent lors de la survenue de symptômes, dont les hallucinations, restait encore débattue (Alderson-Day et al., 2016). Nous avons utilisé une méthode de connectivité effective par '*stochastic Dynamic Causal Modeling*', qui a permis de confirmer que le SN jouait un rôle crucial dans le switch entre DMN et CEN au cours des expériences hallucinatoires. Par ailleurs, cette connectivité était modulée en fonction de l'étape de l'hallucination. En particulier, la période 'ON' a été liée à des afflux sensoriels liés à la réactivation de traces mnésiques, sous l'influence de l'hippocampe (vers le SN), alors

que la période ‘OFF’ était associée à une reprise de contrôle du CEN sur le DMN, en faveur d’un processus volontaire, particulièrement intéressant dans la théorisation des approches psychothérapeutiques et d’empowerment des entendeurs de voix.

ARTICLE 2



fMRI capture of auditory hallucinations: validation of the two-steps method

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fMRI capture of auditory hallucinations: validation of the two-steps method

Abbreviated title: fMRI capture of hallucinatory experiences

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Abstract (234 words)

Our purpose was to validate a reliable method to capture brain activity concomitant with hallucinatory events, which constitute frequent and disabling experiences in schizophrenia. Capturing hallucinations using fMRI remains very challenging. We previously developed a method based on a two-steps strategy including (i) multivariate data-driven analysis of per-hallucinatory fMRI recording and (ii) selection of the components of interest based on a post-fMRI interview. However, two tests still need to be conducted to rule out critical pitfalls of conventional fMRI capture methods before this two-steps strategy can be adopted in hallucination research: replication of these findings on an independent sample and assessment of the reliability of the hallucination-related patterns at the subject level. To do so, we recruited a sample of 45 schizophrenia patients suffering from frequent hallucinations, 20 schizophrenia patients without hallucinations and 20 matched healthy volunteers; all participants underwent four different experiments. The main findings are (i) high accuracy in reporting unexpected sensory stimuli in an MRI setting; (ii) good detection concordance between hypothesis-driven and data-driven analysis methods (as used in the two-steps strategy) when controlled unexpected sensory stimuli are presented; (iii) good agreement of the two-steps method with the online button-press approach to capture hallucinatory events; (iv) high spatial consistency of hallucinatory-related networks detected using the two-steps method on two independent samples. By validating the two-steps method, we advance toward the possible transfer of such technology to new image-based therapies for hallucinations.

Key words: Independent Component Analysis; Interview; Schizophrenia; Hallucinations; fMRI; Reproducibility; Reliability.

Introduction

Validating reliable methods to explore the neural bases of consciousness is a crucial aim in neuroscience. This question has a strong impact on our attempts to correlate brain activation with a given behavioral experience. Here, we would like to illustrate how recent functional magnetic resonance imaging (fMRI) developments allow objective "capture" of the neural correlates of unpredictable and subjective mental events, such as hallucinations. Hallucinations are percepts in the absence of external stimuli (Ey, 1973). In schizophrenia, hallucinations are frequent and may cause long-term disability (Hor and Taylor, 2010). In adults, auditory-verbal hallucinations (AVHs) are most frequent (Andreasen and Flaum, 1991), although hallucinations may occur across every sensory modality (David et al., 2011; Llorca et al., 2016). Anatomical and functional disturbances in both primary and association sensory cortices have been proposed to account for AVHs (Allen et al., 2008; Jardri et al., 2011), but the detection of their occurrence while scanning a participant (hallucination capture methods) has long remained very challenging.

In a first subset of capture studies, AVH occurrences were signaled online by asking the participant to press a response button in the MRI scanner (Dierks et al., 1999; Lennox et al., 2000; Silbersweig et al., 1995; Sommer et al., 2008). The subsequent sequence of self-reports serves as a model for brain activity. Despite the cleverness of this method (later called the "button-press" method), several drawbacks were noted. First, the cerebral activations linked to motor readiness were shown to disturb the acquisition of resting state signals (Bazán et al., 2015). Second, the reliability of this method was questioned due to the poor insight and executive dysfunctions that may exist in patients with schizophrenia (Tan,

2009). Finally, activity related to AVHs may precede the button press (Diederen et al., 2010) and exhibit complex dynamics (Lefebvre et al., 2016).

A second line of capture studies utilized discontinuous acquisition methods (also called the "random-sampling" approach), in which many fMRI volumes were acquired at random intervals. Patients were asked for their sensory experiences immediately after each stop (Shergill et al., 2000, 2001). These two strategies (i.e., "button-press" and "random-sampling") both relied on hypothesis-driven fMRI data analyses in that they were based on patient self-report of AVHs during scanning. This drawback made these approaches particularly vulnerable to a drop in performance in signaling hallucination occurrences.

A third line of studies used more data-driven approaches, such as spatial *independent component analysis* (ICA). Applied to fMRI, this statistical method allows to separate co-activated brain regions without a pre-defined temporal model of brain activity (Formisano et al., 2004). Even though the first studies combined ICA with online self-reports (van de Ven et al., 2005; Jardri et al., 2009), this method mainly paved the way to more simple designs for hallucinating patients, since they were only asked to report AVHs after acquisition, using a post-fMRI interview (Jardri et al., 2007, 2009). Data from this interview was also used to help select the most relevant components among those blindly generated by ICA, i.e., spatial functional patterns that best matched the hallucinations' time of occurrence and phenomenology. We named this approach the *two-steps method for hallucination fMRI capture* (the *"2S"* method), for which a proof-of-concept study has been published (Jardri et al., 2013).

Although promising, two tests still need to be conducted to rule out critical pitfalls of conventional fMRI capture methods before the *"2S"* strategy can be adopted in

hallucinations research: (a) replication of these findings on an independent sample (reproducibility); and (b) assessment of the consistency of the AVH-related patterns at the subject level (reliability). In this article, we addressed these issues by recruiting 85 participants in four different experiments. We successively studied the patients' ability to *a posteriori* report their sensory experiences (i), the concordance between the *"2S"* and the "button-press" methods on controlled stimuli (ii) and on hallucinations (iii), and finally, the consistency of the AVH-related neural networks identified using the *"2S"* procedure on independent samples (iv).

Materials and Methods

Population

We recruited 5 independent samples of participants who were free from any sensory deficit: 20 schizophrenia patients without hallucinations, 20 healthy subjects, and 3 samples of 5, 20 and 20 schizophrenia patients suffering from frequent AVHs. Patients were assigned to the "no-hallucination" group if they had not experienced hallucinations in the week prior to participation (task 1). They were assigned to the "AVH" group if the PANSS P3 item score was ≥ 3, with hallucination experiences frequent enough to occur during an MRI session (tasks 3 & 4). Please note that in task 3, five schizophrenia patients were selected for their good self-report of hallucinatory events (a necessary criterion for using the "button-press" approach) and that in task 4, two different subsets of twenty patients each were recruited to control for the possible influence of age and medication on replicability. The main characteristics of these samples are reported in **Table 1**. All the patients enrolled in tasks 3 only had hallucinations in the auditory modality. For the patients in task 4, 88 % of these experiences occurred in the auditory modality, whereas 35, 12 and 12 % were coenesthetic,

visual and olfactory, respectively. All the participants were recruited at the University Hospital of Lille, except for those participating in task 3, which was performed at the University Hospital of Strasbourg.

Table 1: Characteristics of the enrolled samples (mean+/-sd).

Task	1	2*	3	4*	4
Sample	#1	#2	#3	#4	#5
Number of subjects	20	20	5	20	20
Population	Schizophrenia without hallucinations	Healthy subjects	Schizophrenia with hallucinations	First episode psychosis with hallucinations	Schizophrenia with hallucinations
Sex Ratio	17/3	15/5	3/2	17/3	14/6
Age (years)	39,5 +/- 10	12,9+/-1,6	34,4 +/-9,3	13,1+/-1,8	33,7+/-8,2
Dose of antipsychotic treatment (EqOZ)	20,9 +/- 12,7	0	21,2 +/-10,8	0	36,2+/- 17,3
PANSS-P	13,9+/-4,2	NA	22,8 +/-4,2	29,4+/-5,3	22+/- 4,4
PANSS-P3	1+/-0	1 +/- 0	5,2 +/- 0,4	5,1+/-1,3	5,3+/-0,9
Type of acquisition	MR-simulator	Single shot EPI	Single shot EPI	Single shot EPI	3D-PRESTO
Acquisition time	10 minutes	10 minutes	20 minutes	10 minutes	10 minutes
Sequence parameters					
Echo time (msec)	NA	70	43	70	30
Repetition time (msec)	NA	3000	3000	3000	1000
Voxel size (mm^3)	NA	4	4	4	3.3
Number of scans	NA	300	400	300	900
Acquisition per subject	1	1	4	1	1

EqOZ: *equivalent olanzapine*; PANSS: *positive and negative syndrome scale*; PANSS-P: positive sub-score of the PANSS scale; PANSS-P3: P3 sub-score of the PANSS scale; NA: not available; EPI: *echo-planar imaging*; 3D-PRESTO: *PRinciples of Echo-Shifting with a Train of Observations*; *: Data from Jardri et al., 2013; There was no overlap between the two samples recruited in task 4.

Experimental Procedures

Task 1

Task 1 was designed to determine if schizophrenia patients could *a posteriori* report, with good precision, sensory experiences that occurred in a controlled experimental setting (i.e., using real auditory stimuli, with known characteristics in terms of time of onset, duration, amplitude, etc.). Task 1 was performed in an MRI simulator. We selected patients without AVHs for this first experiment to avoid any confusion in reporting task-related auditory stimuli vs. endogenous percepts (i.e., AVHs). Patients were asked to lie down at rest without falling asleep and were put in a dark environment. They were only asked to report auditory stimuli *a posteriori*. For 10 minutes, the sound of an EPI (e.g. Echo-Planar Imaging) sequence was delivered without real MRI scan acquisition. In complement, a variable number of unexpected auditory stimuli were randomly presented through the headphones using E-Prime 1.3 (*Psychology Software Tools Inc., Pittsburgh, USA*) (normalized amplitude = 75 dB SPL). We used verbal material and selected 0 to 4 voices/participant (male voices, all unknown to the participants), as this is the mean number of AVHs usually reported during an fMRI session (Lefebvre et al., 2016). Stimulus presentations lasted from 6 to 30 seconds. Patients were interviewed immediately after the experiment about what they heard using a post-fMRI questionnaire (see the *Analysis* section). The number of voices heard and the moments of occurrence were reported. Voice detection performance was also measured.

Task 2

Task 2 was designed to evaluate the inter-method reliability of the *"2S"* method compared with detection of controlled stimuli using hypothesis-driven analysis. Task 2 was performed in an MRI scanner. Healthy participants were asked to lie down at rest without falling asleep while wearing MR-compatible headphones that transmitted audible stimuli and attenuated the ambient noise of the scanner. They were only asked to report auditory stimuli *a posteriori*. During the 10-minute fMRI session, a variable number (n) of words or sentences were presented through the headphones using E-Prime 1.3 (*Psychology Software Tools Inc., Pittsburgh, USA*) (normalized amplitude = 75 dB SPL). When compared with task 1, and because the purpose was no longer to test the quality of reporting of the patients, we chose to enhance power by increasing the total number of stimuli presented from [0-4] to [0-10]. Stimulus presentations lasted from 6 to 30 seconds. Patients were interviewed immediately after the experiment about what they heard, using a post-fMRI questionnaire (see the *Analysis* section). The number of heard stimuli and their moments of occurrence were reported. We then compared the *"2S"* method with a general linear model (GLM) built using the exact timepoints of stimulus presentation.

Task 3

Task 3 was designed to evaluate the agreement between capture methods (i.e., between the *"2S"* and the "button-press" methods) in patients with a good self-report of their hallucinatory events. Task 3 was performed in an MRI scanner. The patients were asked to lie down at rest without falling asleep during acquisition. Each patient completed four different 20-minute fMRI sessions. During the first 3 sessions, the patients were instructed

to signal the onset of their hallucinations with a response button (right hand) and to release it when the hallucinations stopped, i.e. they were explicitly asked to report hallucinations online which has been referred to as the "*button-press*" condition. In the last session, the *"2S"* procedure was applied, and the patients were interviewed immediately after this last acquisition about what they heard, using a post-fMRI questionnaire (see the *Analysis* section). The number of AVHs and their moments of occurrence were reported.

Task 4

Task 4 was designed to test the reproducibility of the *"2S"* procedure. Task 4 was performed in an MRI scanner. Patients with AVH were asked to lie down at rest without falling asleep during acquisition. They were only asked to report hallucinations *a posteriori*. Each patient had a 10-minute fMRI session, and the *"2S"* procedure was applied to identify AVH periods during scanning. Two complementary analyses were conducted. First, we computed the spatial similarity between the AVH-related functional brain networks obtained at the subject level. Second, the between-sample consistency in hallucination detection between the current dataset and a previous independent sample (Jardri et al., 2013) as well as with coordinate-based meta-analytic findings from 10 different studies (Jardri et al., 2011) (Cf. **Table 1**) was evaluated for the hallucination-related network (association sensory cortices, ASC) (Jardri et al., 2013) and the default mode network (DMN), which is considered a standard, well-replicated and ubiquitous neural network.

Analyses

A posteriori voice detection performance

This analysis used the data collected in task 1. To normalize performance across subjects, sensitivity was recorded as 1 if all the voices were detected, and specificity was recorded as 1 if there were no additional recognized sounds. In all other cases, sensitivity and specificity were recorded as 0. We further generated random data for 20 mock participants and matched these data with those of the patients according to the number of voices presented. We generated random detection values using the RAND function (in *Matlab R2016a*). Each simulated recording was randomly divided into periods with and without voices, and a number of 0 or 1 was randomly assigned to each. Then, as for the patients, if the number was 1 for all of the periods with voices, a sensitivity of 1 was reported. If the number was 0 for all of the periods without voices, the specificity was 1. Accuracy was defined as (true detection + true no detection) / (true detection + false detection + true no detection + false no detection). The patient and simulated data were compared using a permutation test with an α level of 0.05 using *R software for statistical computing* v3.3. The patient and simulated data were compared using a two-samples permutation test with 1000 iterations (Monte Carlo method) and an α level of 0.05, performed using the 'perm' package with R software for statistical computing v3.3.

The two-steps hallucination fMRI capture procedure

This analysis was conducted on data collected in tasks 2, 3 and 4. Our capture method is divided into two consecutive steps (Jardri et al., 2013) (cf. **Figure 1a, Supplementary figure 1**). This method was developed to capture unpredictable events, such as hallucinations and

unexpected stimuli presented to healthy participants. Step 1 is resting-state fMRI acquisition in participants with or without AVHs. Step 2 occurs immediately after MRI acquisition. Using a standardized post-fMRI interview, each participant is asked to report all the sensory experiences that occurred during scanning, including the sensory modality and number of events as well as their approximate times of occurrence (a translated version of the interview is available by request to the corresponding author).

Conventional preprocessing steps were conducted on anatomical and functional data (as detailed in our previous publications, (Jardri et al., 2013; Lefebvre et al., 2016). Functional data were preprocessed using a slice scan time correction, a 3D head motion correction, smoothing using a spatial Gaussian filter (full-width at half-maximum [FWHM] = 6.0 mm), a temporal high-pass filtering with 2 sin/cos, and linear trend removal. The anatomical data were submitted to an intensity inhomogeneity correction algorithm, resampled to a 0.5 mm^3 resolution, and normalized in Talairach's stereotactic space (Talairach J, Tournoux P, 1988). Data from the head tissue, subcortical structures, and cerebellum were then removed with the aim of advanced cortical segmentation processing. This segmentation was performed at the gray/white matter and the gray matter/cerebrospinal fluid boundaries. A Boundary-based registration was finally used to align the functional/anatomical data-sets.

Data obtained from step 1 are first blindly analyzed using cortex-based ICA analysis (Formisano et al., 2004). For each patient, cb-ICA (using the spatial decomposition algorithm "FastICA" (Hyvärinen and Oja, 2000)) is used to extract (20% of the total volume) independent components (ICs) from the rs-fMRI signal of the cortical voxels of the matrix, i.e., 30 ICs for task 2 and task 4 and 40 ICs for task 3. We referred to a fixed-point ICA algorithm, i.e., FastICA, which minimizes the mutual information of the components using a

robust approximation of the negentropy as a contrast function and a fast, iterative (nonadaptive) algorithm for its maximization. The deflation approach was used to run FastICA, as previously described by Hyvärinen et al. (1999) and Formisano et al. (2004). The resulting ICs corresponded to 3D clusters of voxels with |Z|-normalized values greater than 2.5. Among these ICs, the most relevant are first selected using the IC-fingerprint method (De Martino et al., 2007; Jardri et al., 2013). Because ICA does not naturally order the resulting components according to their relevance, we referred to the IC-fingerprint method, which jointly uses 7 spatial and temporal signal properties for IC classification purposes (de Martino, 2007). These properties were measured post hoc for each IC to preserve the "data-driven" character of the analysis. This step allowed to discard noise-related ICs (e.g., EPI susceptibility, motion artefacts, high-frequency noise...), to only keep the components related to a neurophysiological source, which were characterized by a high spatial and temporal structure (i.e., degree of clustering and one-lag serial auto-correlation, respectively) and by a high entropy, coupled with a maximum power contribution in the low-frequency range (0.01 Hz - 0.1 Hz) (Roquet et al., 2014). This allows one to retain only the components related to a neurophysiological source (BOLD) for the next step. The surviving ICs are then compared to the post-fMRI interview data, in terms of number, times of occurrence, and functional networks of interest (e.g., speech-related for AVHs, etc.). Data preprocessing, cortex-based ICA and IC-fingerprinting were performed using *Brain Voyager* v20.2.

Inter-method reliability in fMRI stimulus detection

This analysis used the data collected in task 2. Two parallel analyses were applied to the fMRI data in *Brain Voyager*: 1) the *"2S"* analysis, as described in the previous section and based on cb-ICA; 2) a general linear model (GLM) fitted to the experimental protocol generated for each participant using *E-Prime*. This GLM was based on controlled stimulus timing, as the time of stimulus presentation was known *a priori*. Because of the massive univariate nature of GLM analysis applied to fMRI data, the resulting statistical maps were thresholded using a false discovery rate approach ($q < 0.01$, (Genovese et al., 2002)). In addition to conventional correlation analysis, which we considered insufficient to confirm agreement of the results of the two analyses for the same dataset, we performed Deming regression (Cornbleet and Gochman, 1979) to account for observation errors on both the x- and y-axes (i.e., on the BOLD dynamics from GLM and cb-ICA, respectively).

Inter-method reliability in fMRI AVH capture

This analysis was based on data collected in task 3 and used *Matlab R2012b* with the *SPM8, statistical non-parametric mapping (SnPM) and FMRLab v2.3* toolboxes. For the "button-press" condition, we referred to the GLM approach described in the previous section. The brain activity expected to be related to AVHs was modeled by convolving the box-car time course of the button-press from the participants with the canonical hemodynamic response function (HRF), i.e. a two-gamma function using SPM standard parameters. This procedure was used to determine the BOLD-related component with the highest correlation coefficient between its temporal vector and the subject's signaling. As we previously reported that "button-press" components in the same subjects were highly reproducible, they were averaged for each patient (Foucher, 2013). For the *"2S"*

condition, we referred to the ICA approach described in the "two-steps hallucination fMRI capture procedure" section.

Although a high spatial correlation coefficient can be considered a measure of inter-method reliability, here, we used Cohen's kappa coefficient, κ, to assess whether this agreement remains true at the voxel level. The *"button-press" spatial components* and *"2S" spatial components* were successively thresholded at z = 1.5, 2, 2.6, 3 and 3.6 to make binary maps of 0 = [no-AVH voxel], 1 = [AVH voxels] to measure the κ coefficient. Last, possible systematic differences between the spatial *"button-press" components* and *"2S" components* were assessed using a multi-subject pseudo-paired t-test design with SnPM. A permutation test was adopted due to the limited number of subjects in this task. Significance was set at pseudo-t > 2 with an extension k > 1 cm^3 (125 voxels) within the regions of interest, which were defined as regions that were positively active in either the signaling or resting condition, i.e., "button-press" or *"2S"* component.

Spatial consistencies in hallucination detection

This analysis used the data collected in task 4 (samples #4 & #5). After a first-level analysis (based on the *"2S"* capture method) was conducted, a secondary analysis was conducted by submitting individual ICs to a self-organizing group IC algorithm (*sog-ICA*, Esposito et al., 2005). An iterative cluster-size thresholding procedure based on Monte Carlo simulations (n = 1000) further corrected the resulting random-effects statistical maps, which were used to evaluate the regional stability of these AVH-related neural networks.

Between-subjects' spatial consistency was first tested using multidimensional similarity clustering (MDS) on sample #5 (See **table 1**). The MDS algorithm was applied on the sog-ICA decomposition of per-hallucinatory fMRI data, and the MDS linear projections were plotted in 2-dimensional space (Torgerson, 1952) in *Brain Voyager 20.2*. To help

identify cluster plots of interest, the random-effects sog-ICA validation maps were visualized using the same color codes.

Between-samples spatial consistency was also tested using probabilistic mapping between sample #4 (Jardri et al., 2013) and #5 (replication sample). Note that these independent samples were obtained from different scanners using different sequences (single-shot EPI and 3D-PRESTO, respectively) and different magnetic fields strength (1.5T and 3T, respectively) (Cf. **Table 1**). At each spatial location, functional maps were generated to represent the relative number of subjects leading to significant activation patterns within the networks of interest for the initial sample (#4 (Jardri et al., 2013), n = 20), the replication sample (#5, n = 20), and coordinate-based meta-analytic findings (Jardri et al., 2011).

Linear regression analysis between default mode and AVH-related signal time courses

This analysis used the data collected in task 4. The AVH-related ICs were selected using samples #4 (Jardri et al., 2013) and #5 (task 4) according to the *"2S"* procedure. In parallel, we used the same data sets and selected ICs related to the DMN using a "goodness-of-fit" (GoF) procedure. For each participant, the IC with the highest GoF score (i.e., absolute correlation coefficient with a DM template taken from Laird et al., 2009 (Laird et al., 2009)) was assumed to be the DM component. To explore the dynamics of the AVH-related and DM-related networks, we normalized their fMRI signals to relative variations with respect to the mean value of the participants' individual time series (Deco et al., 2009). AVH-related and DM-related networks signal fluctuations were compared using the Pearson product moment correlation in samples #4 (Jardri et al., 2013) and #5, respectively.

Ethical issues/ study ID

All patients gave written informed consent. The study ID for task #3 is CPP03/45-PSY 2003/52S, while that for tasks #1, 2, and 4 is 2009-A00842-55. All reported experiments performed by the authors complied with Helsinki declaration and its amendments.

Results

Are schizophrenia patients able to report with precision sensory experiences *a posteriori* (task 1)?

We tested the ability of schizophrenia patients to report off-line unexpected sensory events and their times of occurrence in the scanning context. The accuracy of a posteriori voices labelling in schizophrenia patients was measured at 95% ($^{95\%}$IC = 85.3-99.9), while random detection for 0 to 4 events would be 20% ($^{95\%}$IC = 9.61-36.14). This difference was highly significant (permutation testing, mean difference = 77.5, p = 0.002; Cf. **Figure 1b**). Sensitivity was 100% ($^{95\%}$IC = 80.0-100) and specificity was 95% ($^{95\%}$IC = 0.73-99.7), while random detection for 0 to 4 events would be 20% ($^{95\%}$IC = 6.61-44.3) for both.

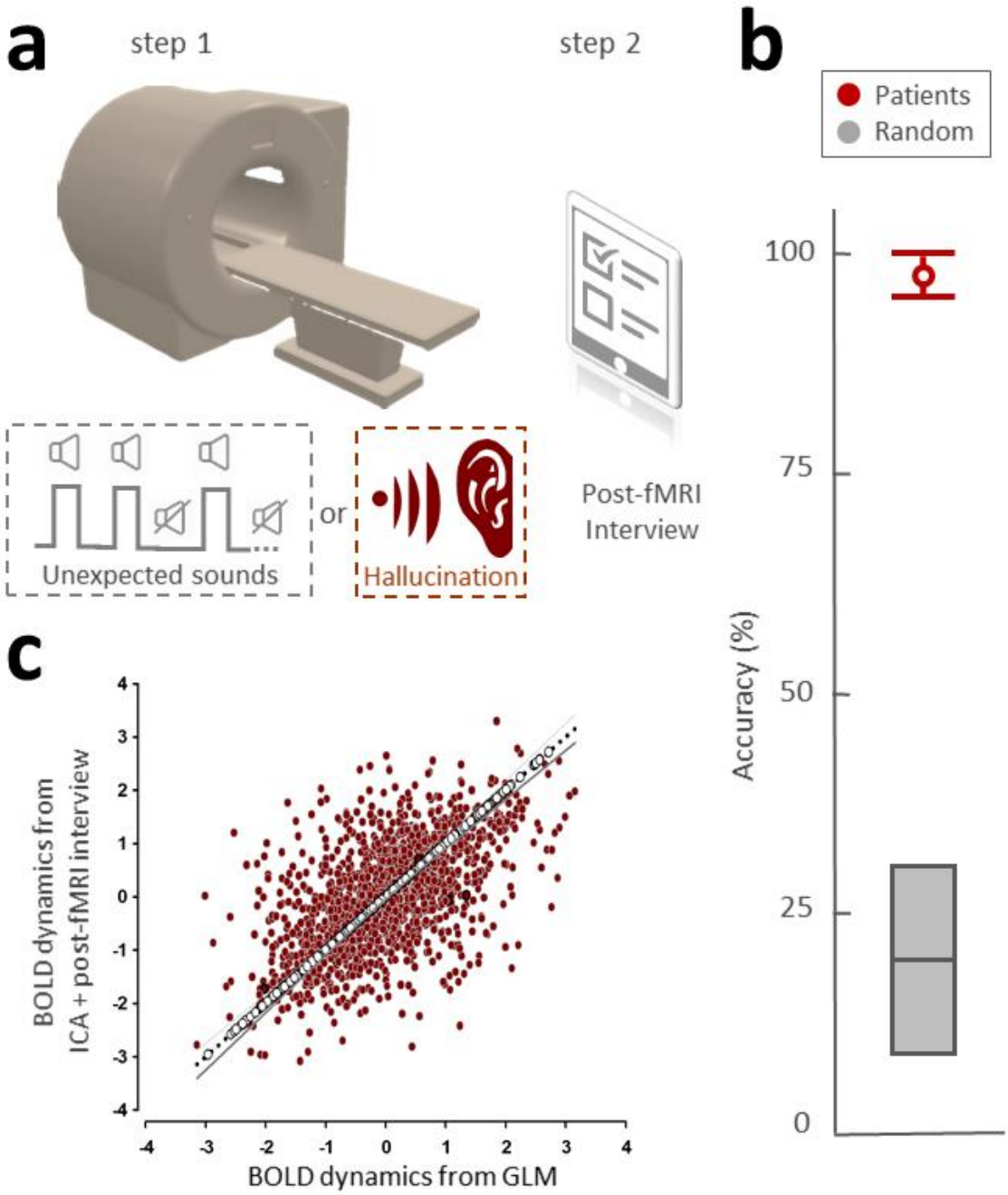

Figure 1. **The hallucination capture method**. ***a) Description of the two-steps procedure***. Step 1 occurs while participants are laying down in the MRI scanner. Two populations were tested with a variation on step 1: (i) healthy participants, who were exposed to unexpected voices during scanning (grey dotted square); and (ii) schizophrenia patients with frequent hallucinations, who were scanned without stimulus presentation because hallucinations constitute internally generated percepts (red dotted square). Step 2 occurs immediately after MRI acquisition. Using a standardized post-fMRI interview (see Methods), participants were asked to report sensory experiences that occurred during scanning as well as their precise

time of occurrence. The collected data were then used to select the most appropriate components resulting from blind multivariate analysis of the fMRI signal (cortex-based independent component analysis or ICA). The results for healthy volunteers (n = 20) are presented in Figure 1c, while those for hallucinators (n = 20) are presented in Figures 3 and 4. ***b) Task 1: The ability of schizophrenia patients to report off-line the number of sensory events and their times of occurrence***. Twenty new patients without hallucinations were also tested using the "unexpected voices" procedure in an fMRI simulator. The accuracy of a posteriori sound labeling in the schizophrenia patients was plotted in red (mean 97.5%; $^{95\%}$IC = 85.3-99.9), while random detection for 0 to 4 events would be 20% ($^{95\%}$IC = 9.61-36.14, grey). Mean difference = 77.5, p = 0.002. ***c) Task 3: Validation of ICA + interview versus gold standard analysis***. Two parallel analyses (i.e., ICA + interview and general linear model analysis using the sound presentation protocol) were conducted on the same healthy volunteer dataset. Deming regression analysis was used to account for observation errors on both the x- and y-axes (r = 0.57, with a test for slope $F_{2,98}$ = 2.1; p < 0.0001) and confirmed the high degree of precision of our capture method, even in the absence of online report.

<u>Inter-method reliability in detecting controlled auditory stimuli (task 2)</u>

A Deming regression analysis was used to account for observation errors on both the x- and y-axes (r = 0.57, with a significant test for slope $F_{2,98}$ = 2.1; p < 0.0001), and confirmed the high degree of precision of the *"2S"* method even in the absence of online report, as shown by the good agreement with the GLM analysis based on controlled stimuli (Cf. **Figure 1c**).

Inter-method reliability in detecting online AVHs (task 3)

The average spatial correlation coefficient between the *"2S"* and "button-press" components was r = 0.68 $\pm$ 0.1 (Cf. **Figure 2a**). The average Cohen's kappa coefficient was 0.50 $\pm$ 0.08 and was relatively consistent regardless of the z-score threshold. **Figure 2b** shows the plot of each individual κ according to the z-score threshold. The SnPM comparison between the *"2S"* and "button-press" spontaneous activity maps did not provide any evidence of a significant difference despite the use of a lenient threshold (Cf. **Figure 2c**).

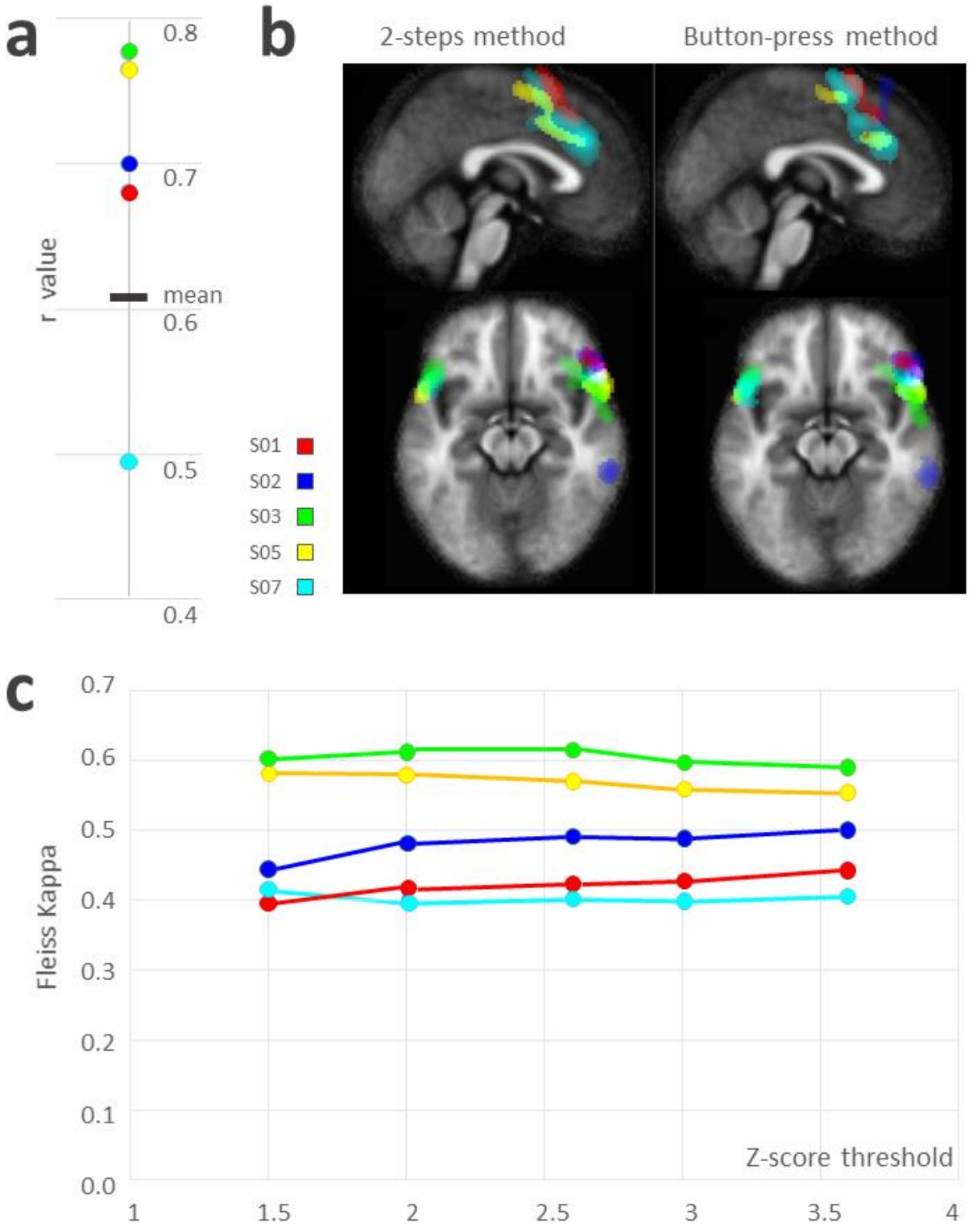

Figure 2. Task 2: Inter-method reliability in auditory-verbal hallucination (AVH)-related networks. Five schizophrenia patients with refractory hallucinations underwent four different 20-minute sessions of 400 single-shot EPI fMRI. During the 3 first sessions, they were instructed to signal the onset of an AVH with a response-button (right hand) and to release it when the AVH stopped. In the last session, the patients were instructed to lie

down with their eyes closed without falling asleep. At the end of this session, they completed a post-fMRI interview to precisely report the times AVHs occurred during the scan. Components of interest were detected using the "button-press" method for the 3 first sessions and then averaged, while they were detected using the "*two-steps" (2S)* method for the last session. Each color represents one of the five patients. **a)** Correlation between the "*2S"* and the "button-press" methods for each participant; **b)** Components of interest chosen during AVH experiences for each participant using the *"2S"* and the "button-press" methods. **c)** Fleiss's kappa value, i.e., intersession concordance according to different statistical thresholds for SPM analysis.

Reproducibility of neural networks identified during AVHs (task 4)

After MDS projection, four main clusters were identified; these clusters represented the sensorimotor network (cluster 1), the AVH-related network (cluster 2), the salience network (cluster 3), and the visual rest network (cluster 4) (Cf. **Figure 3a**). Random-effects activation maps resulting from sog-ICA are presented in a glass brain (Cf. **Figure 3b**). The AVH-related network encompasses widespread cortical-subcortical areas, as listed in **Table 2**.

Table 2. Regions involved in the hallucination-related network after the group-ICA decomposition of per-hallucinatory fMRI data.

Identified Clusters	Talairach and Tournoux Coordinates (x,y,z)	Number o
Right Cerebrum, Sub-lobar, Insula	41, 8, 5	10850
Left Cerebellum, Anterior Lobe, Culmen	-2, -59, -9	7104
Left Cerebrum, Sub-lobar, Insula,	-47, 8, 4	7069
Left Cerebrum, Parietal Lobe, Inferior Parietal Lobule	-55, -30, 36	6078
Right Cerebrum, Limbic Lobe, Cingulate Gyrus,	2, 23, 31	4152
Right Cerebrum, Frontal Lobe, Sub-Gyral	21, -7, 57	3079
Left Cerebrum, Frontal Lobe, Middle Frontal Gyrus	-28, 47, 22	1763
Left Cerebrum, Occipital Lobe, Lingual Gyrus	-19, -85, -4	1335
Right Cerebrum, Occipital Lobe, Middle Occipital Gyrus	34, -85, 9	1253
Right Cerebellum, Anterior Lobe, Culmen	46, -37, -28	1021
Right Cerebrum, Limbic Lobe, Uncus	27, 10, -25	943
Left Cerebrum, Frontal Lobe, Inferior Frontal Gyrus	-16, 21, -16	923
Left Cerebrum, Occipital Lobe, Cuneus	-16, -91, 14	740
Right Cerebrum, Frontal Lobe, Sub-Gyral	18, 28, -14	700
Left Cerebellum, Posterior Lobe, Cerebellar Tonsi	-36, -55, -39	653
Left Cerebrum, Occipital Lobe, Middle Occipital Gyrus	-36, -72, -7	574
Right Cerebellum, Posterior Lobe, Inferior Semi-Lunar Lobule	7, -76, -39	540
Right Cerebrum, Temporal Lobe, Transverse Temporal Gyrus	54, -18, 11	522
Left Cerebrum, Limbic Lobe, Uncus	-18, 5, -22	406

Data indicate x-y-z coordinates in stereotaxic space (TAL) of the weighted center for each identified cluster as well as the total number of voxels.

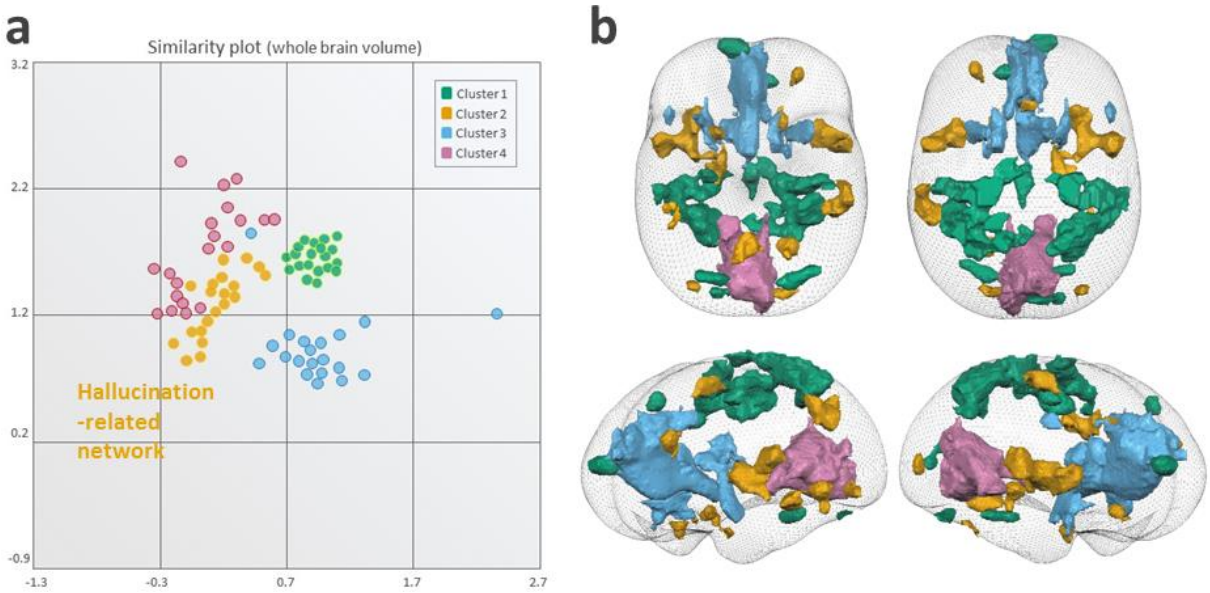

Figure 3. Task 4: Between-subjects' spatial consistency in auditory-verbal hallucination (AVH) detection (n = 20). **a)** *Cluster plots identified after multi-dimensional similarity clustering projection.* Each circle represents an individual IC taken from the 20 enrolled schizophrenia patients who experienced AVHs while scanning. Four clusters were identified and represented the sensorimotor network (cluster 1, green), the AVH-related network (cluster 2, orange), the salience network (cluster 3, blue), and the visual rest network (cluster 4, purple), **b)** *Random-effects activation maps* resulting from self-organizing group ICA presented in a glass brain, with colors assigned according to the cluster plot (shown in a). The AVH-related network is plotted in orange and encompasses the precentral gyrus, culmen, insula, inferior parietal lobule, cingulate gyrus, middle frontal gyrus, superior frontal gyrus, middle occipital gyrus, inferior frontal gyrus, cerebellar tonsil, fusiform gyrus, inferior semi-lunar lobule, transverse temporal gyrus and limbic lobe.

In a second step, we overlaid the results of the replication sample (2016) with those of the 2013 sample and with coordinate-based meta-analytic findings. At the group level, a negative correlation was identified between the BOLD signal of the AVH-related and DM-related networks, in both the 2013 sample ($r^2 = 0.38$, $p < 0.0001$; taken from Jardri et al. (2013)) and the current 2016 replication sample ($r^2 = 0.39$, $p < 0.0001$; Cf. **Figure 4a**). The spatial consistencies in the AVH-related and DM functional networks across these two independent samples of hallucinators (2013 and 2016) and with coordinate-based meta-analytic findings were also computed (Cf. **Figure 4b-c**). Important overlap was evident within the ASC and the DMN network.

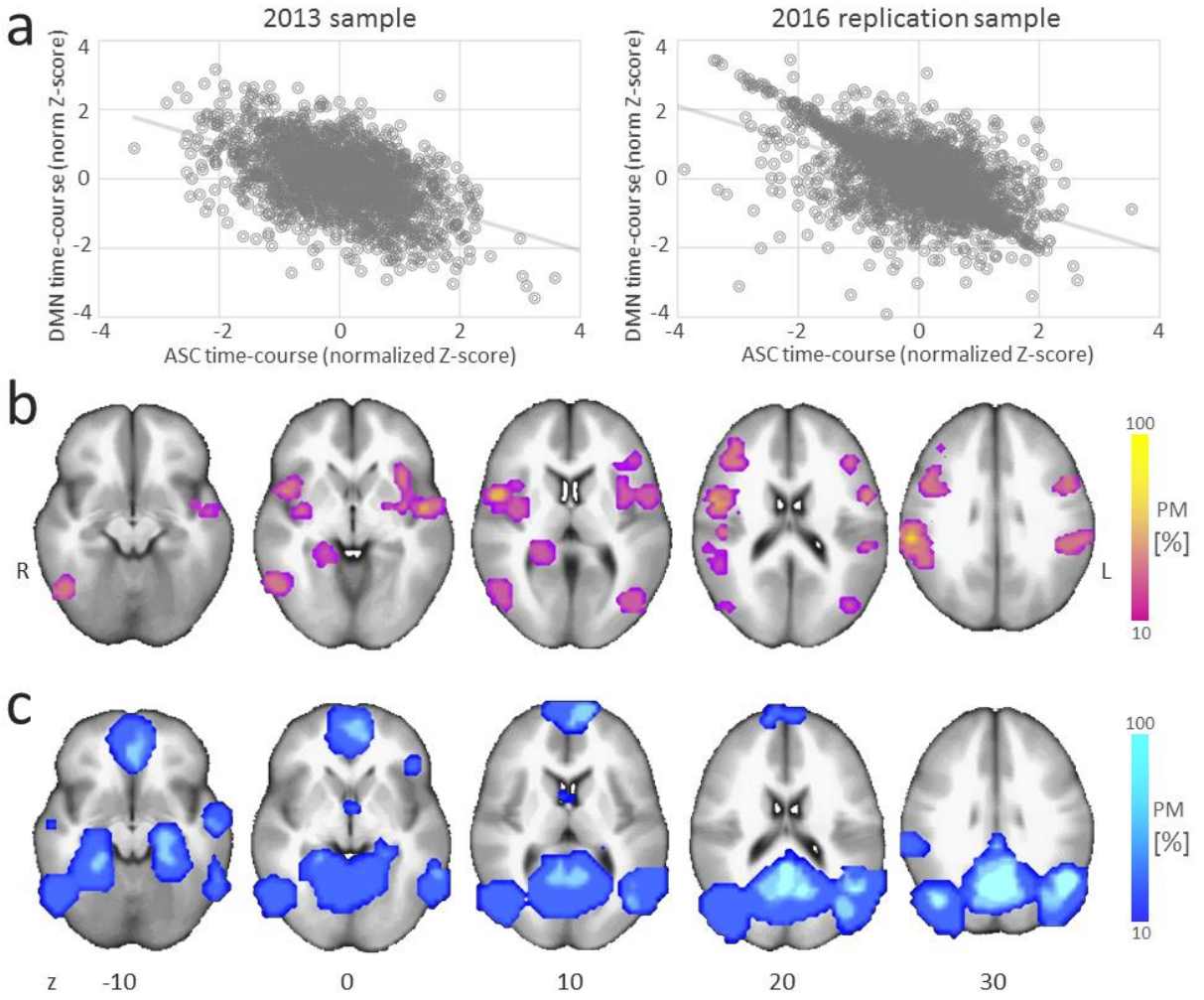

Figure 4. Task 4: Between-sample consistency in auditory-verbal hallucination (AVH) detection. a) At the group-level, a negative correlation was observed between the AVH-related network (within association cortices, ASC) and the default mode network (DMN) BOLD fluctuations, in both sample #4 (taken from Jardri et al., 2013) and the current 2016 replication sample (#5). **b, c)** Spatial consistency in AVH-related and DM-related functional networks across the two independent samples of hallucinators (#4 and #5). At each spatial location, functional maps represent the relative number of subjects leading to significant activation patterns within the networks of interest for the initial sample (#4, 2013, n = 20) and the replication sample (#5, 2016, n = 20) as well as for coordinate-based meta-analytic findings for hallucination capture **(b)** and for the anti-correlated DMN **(c)**. PM: probabilistic mapping; R/L indicate the right/left hemispheres.

Discussion

A major drawback in fMRI capture methods today remains the absence of a gold standard in detecting hallucinations during scanning. Because hallucinations are complex sensory experiences (David et al., 2011) that are often associated with negative affective states, reporting these symptoms online quickly becomes very challenging in the context of an MRI examination, especially for the most disabled patients. The subjects included in such studies are indeed specifically selected for their ability to report their symptoms online. Thus, to extend AVH capture to the field of clinical applications, developing a method applicable whatever the age and AVH severity appears critical.

Despite its limitations, fMRI capture of hallucinations based on online self-reports received some validations in the literature (e.g., Sommer, 2008). Using a button-press approach, Diederen et al. (2013) notably confirmed the good reproducibility in brain activations obtained through fMRI capture of AVHs after two scans. Using a meta-analytical approach, the same group also compared the brain activity measured during auditory stimulus detection with the activity concomitant to AVH (van Lutterveld, 2013). These authors were able to disentangle specific activation related to AVH from the spatial patterns associated with button-press signaling. Interestingly, previous works emphasized the pertinence of ICA-based approaches, and their compatibility with button-press methods. In a study that combined ICA with online self-reports, van de Ven et al. (2005) demonstrated that a positive correlation exists between the average BOLD time-course obtained from the positive voxels of the component of interest and the button press reference model. Using a similar approach, Foucher (2013) showed the superiority of ICA over GLM for the analysis of the “button-press” method of hallucination capture. These encouraging findings paved the

way for the assessment of inter-method reliability, external consistency and quality of sensory experiences report in patients with hallucinations as reported here.

Our purpose was thus to validate the *"2S"* method for fMRI hallucination capture, as initially introduced in a previous paper from our group (Jardri et al., 2013). The use of a post-fMRI interview proved capable of detecting a large range of modality-dependent experiences, without needing to put the participant in a dual-task situation (i.e., experiencing vivid hallucinations and at the same time pressing a response button). Several lines of support for the *"2S"* approach emerged from the present experiments. In a behavioral task, we first showed that schizophrenia patients were able to report controlled unexpected auditory stimuli with high accuracy in an fMRI environment. Using the same task while scanning healthy participants, we also demonstrated good concordance between a model-based analysis and the *"2S"* approach, which combined blind fMRI analysis with a post-fMRI interview. In a third experiment, we confirmed good agreement between the *"2S"* and online button-press approaches to capturing AVHs. Finally, the neural networks (e.g., AVH-related and DM-related networks) detected using the *"2S"* strategy in two independent samples were found to be highly comparable, supporting the good reproducibility of this method.

We showed in task 1 that despite the presence of an invalidating disorder, patients were fully able to *a posteriori* report the occurrence of unexpected voices presented during an MR simulation session. The reliability of the patients' report was very high despite very restrictive statistical analysis (if a patient did not recognize one voice out of all of the voices presented, she/he was considered "not able to report"). This result constitutes the first level of validation for the post-fMRI interview in a population of schizophrenia patients. In the

second task, we evaluated the reliability of the *"2S"* method compared with GLM analysis of controlled stimuli in healthy subjects and confirmed the high degree of precision of the *"2S"* method in a real fMRI setting, even without online report.

Based on the analysis of repeated scans in patients suffering from hallucinations, we further evidenced the stability of data obtained using the *"2S"* procedure and the conventional button-press approach in patients who were able to signal AVHs online. To date, the "button press" method is the most common accepted method, but it has important limitations, as previously listed (mainly due to motor readiness, executive dysfunction in schizophrenia, and the complex neural dynamics of AVHs). Consequently, we could only include 5 patients with good insight who were able to report their sensory experiences online (task 3). In contrast, we expect the *"2S"* method to be applicable to all patients with schizophrenia (we were able to recruit larger samples for tasks 2 and 4 for instance). The simplicity of the experimental setting of the *"2S"* method also constitutes an advantage over other capture methods, especially for patients who could have difficulties reporting hallucinations online, such as older participants or children (see, for example, Jardri et al. (2007)). Overall, tasks 1-3 confirmed the feasibility and reliability of the *"2S"* method despite the use of a post-fMRI interview. These results are important since a key strength, but also a potential limit of the *"2S"* method, specifically resides in the *a posteriori* nature of our interview. This question constitutes a hot but still unresolved topic in consciousness research.

Indeed, two types of methods have been proposed in experiments that test conscious access: (i) *report-based* paradigms and (ii) *no-report* paradigms (Tsuchiya et al., 2015), such as those based on eye-tracking methods. Crucially, no-re*port* paradigms could

overestimate the occurrence of AVH-linked neural activation by including activation that occurs just before or after the activation directly related to hallucinations. These activations could be linked to post-perceptual processes (i.e., cognitive processes) or pre-perceptual processes (i.e., pre-neural correlates of AVHs) (Overgaard and Fazekas, 2016). Moreover, the occurrence of AVHs remains strongly subjective and patient dependent, even though we were able to demonstrate good reproducibility in the current study. Currently, we have no reason to prefer subjective variation linked to the operator in *no-report* paradigms to the individual variation observed in *report-based* paradigms. Furthermore, *report-based* paradigms could underestimate AVH occurrences because AVHs are linked to cognitive processes such as attention, working memory, decision making, and action planning. For example, reduced reporting was observed in the context of inattentional amnesia or experience without access (Tsuchiya et al., 2015). Here, our goal was to validate a method for reporting conscious experiences with good reliability and to correlate them with neural activations. By combining the use of a *report-based paradigm* (i.e., the interview) and a *no-report* paradigm (i.e., blind fMRI analysis), the *"2S"* fMRI capture method appears fully compatible with recent recommendations on conscious access paradigms to limit issues related to the unpredictable nature of the events of interest (Tsuchiya et al., 2016). We think interesting in the near future to test if the fMRI-based approach described in this paper could be extended to other spontaneous phasic mental events, such as obsessions and tics.

We also studied the internal and external consistency of the results found using the *"2S"* procedure by testing the degree of overlap between (i) the cortical areas associated with AVH experiences as reported in the literature (Jardri et al., 2011) and (ii) the results obtained in two independent samples of hallucinators (in 2013 and 2016). The overlap was

maximal within association cortices (ASC); these areas, including the insula and temporo-parietal junction, are known to play a core role in AVH experiences (Jardri et al., 2011). Interestingly, in these datasets, a similar degree of overlap was found for well-replicated intrinsic connectivity networks (Laird et al., 2009), such as the DMN. The negative correlation in BOLD fluctuations between the AVH-related and DM-related networks found in sample #4 (Jardri et al., 2013) was replicated in sample #5. By replicating previous findings, these results provide further support for the existence of anticorrelation between the DMN and sensory cortices during AVH experiences and of a central role of DMN dynamics in these phenomena (Alderson-Day et al., 2016; Lefebvre et al., 2016). This finding allows us to add the anticorrelation of DM-related/AVH-related time courses as a complementary selection criterion for the component of interest in the *"2S"* method (Lefebvre et al., 2016). These findings reinforce the consistency of the method as applied to fMRI capture of hallucinations. The overlap in the speech-related network and in the hippocampal complex was up to 90% and 65%, respectively, supporting the previously suggested core role of these areas in hallucinations (Allen et al., 2012; Amad et al., 2014). In contrast, other areas in this network may reflect the phenomenological content of the experiences, which is only shared by a minority of hallucinators (Ffytche et al., 1998; Jardri et al., 2013).

Importantly, the use of different samples of patients recruited from different centers as well as different scanners with various MR field strengths and fMRI sequences constitutes a strength of this paper. Although some of the patients came from the same center (CHU Lille), we avoided overlap between the samples involved in the different tasks. Heterogeneity in terms of age or symptom severity between the tasks further supports the reliability of the *"2S"* method in various populations, including patients who could have poor

reporting ability, such as adolescents experiencing acute psychosis or adults suffering from severe chronic schizophrenia. This approach is further strengthened by the reference to multivariate statistics, such as ICA, which enables better control of false-positive rates compared to conventional massive univariate approaches (GLM) (Eklund et al., 2016) while also providing access to effect-size estimates (i.e., fMRI changes during hallucinations at the component level), a criterion recently recommended for good practice in fMRI research (Chen et al., 2017).

From a methodological point of view, ICA presents several advantages in the context of fMRI capture of hallucinations. A first one relies in the use of multivariate statistics. Interestingly, the performance of such algorithms seems to substantially benefit from dimensionality reduction (Formisano et al, 2004) compared to more massive univariate methods. Indeed, we made the choice to perform a cb-ICA, based on the idea that only 20% of the voxels lie within the cortex. Readers should stay aware that hallucinations may involve complex cortical-subcortical interactions (e.g., Hoffman et al, 2011). However, our choice to restrict analyses to the part of the matrix containing cortex stays justified in the context of target definition for neuromodulation tools. Again, considering that hallucinations may result from neural dysconnectivity (e.g., Curcic-Blake et al, 2017) favors ICA over more conventional activation-based approaches, like GLM. Here, the ICA decomposition of time-series provides a direct equivalent of functional connectivity components, more in line with the process we want to capture.

Finally, we believe that the *"2S"* method may have crucial therapeutic implications in the near future, notably, in optimizing strategies for repetitive transcranial magnetic stimulation (rTMS) for refractory hallucinations. Although this non-invasive brain stimulation

method has shown moderate, but significant, efficacy in reducing the severity of hallucinations (Demeulemeester et al., 2012), it remains a source of debate (Slotema et al., 2011). Its moderate effect may result from inter-subject variation in the brain areas associated with AVH, since most rTMS protocols systematically target the left temporo-parietal junction. Identifying with high reliability the functional networks recruited during AVH in a given individual could pave the way for new subject-based neuronavigation strategies for rTMS treatment of hallucinations. A randomized controlled trial is currently running to test the superiority of such an fMRI-guided strategy over conventional rTMS in the treatment of drug-resistant hallucinations (ClinicalTrials.gov Identifier: NCT01373866).

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References

Alderson-Day B, Diederen K, Fernyhough C, Ford JM, Horga G, Margulies DS, McCarthy-Jones S, Northoff G, Shine JM, Turner J, van de Ven V, van Lutterveld R, Waters F, Jardri R (2016) Auditory Hallucinations and the Brain's Resting-State Networks: Findings and Methodological Observations. Schizophr Bull 42:1110–1123.

Allen P, Larøi F, McGuire PK, Aleman A (2008) The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. Neurosci Biobehav Rev 32:175–191.

Allen P, Modinos G, Hubl D, Shields G, Cachia A, Jardri R, Thomas P, Woodward T, Shotbolt P, Plaze M, Hoffman R (2012) Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. Schizophr Bull 38:695–703.

Amad A, Cachia A, Gorwood P, Pins D, Delmaire C, Rolland B, Mondino M, Thomas P, Jardri R (2014) The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations. Mol Psychiatry 19:184–191.

Andreasen NC, Flaum M (1991) Schizophrenia: the characteristic symptoms. Schizophr Bull 17:27–49.

Bazán PR, Biazoli CE, Sato JR, Amaro E (2015) Motor Readiness Increases Brain Connectivity Between Default-Mode Network and Motor Cortex: Impact on Sampling Resting Periods from fMRI Event-Related Studies. Brain Connect 5:631–640.

Chen G, Taylor PA, Shin Y-W, Reynolds RC, Cox RW (2017) Untangling the relatedness among correlations, Part II: Inter-subject correlation group analysis through linear mixed-effects modeling. NeuroImage

Cornbleet PJ, Gochman N (1979) Incorrect least-squares regression coefficients in method-comparison analysis. Clin Chem 25:432–438.

Ćurčić-Blake B, Ford JM, Hubl D, Orlov ND, Sommer IE, Waters F, Allen P, Jardri R, Woodruff PW, David O, Mulert C, Woodward TS, Aleman A (2017): Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. Prog Neurobiol 148:1–20.

David CN, Greenstein D, Clasen L, Gochman P, Miller R, Tossell JW, Mattai AA, Gogtay N, Rapoport JL (2011) Childhood onset schizophrenia: high rate of visual hallucinations. J Am Acad Child Adolesc Psychiatry 50:681–686.e3.

Deco G, Jirsa V, McIntosh AR, Sporns O, Kötter R (2009) Key role of coupling, delay, and noise in resting brain fluctuations. Proc Natl Acad Sci U S A 106:10302–10307.

De Martino F, Gentile F, Esposito F, Balsi M, Di Salle F, Goebel R, Formisano E (2007) Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. NeuroImage 34:177–194.

Demeulemeester M, Amad A, Bubrovszky M, Pins D, Thomas P, Jardri R (2012) What is the real effect of 1-Hz repetitive transcranial magnetic stimulation on hallucinations? Controlling for publication bias in neuromodulation trials. Biol Psychiatry 71:e15–e16.

Diederen KMJ, Charbonnier L, Neggers SFW, van Lutterveld R, Daalman K, Slotema CW, Kahn RS, Sommer IEC (2013) Reproducibility of brain activation during auditory verbal hallucinations. Schizophr Res 146:320–325.

Diederen KMJ, Neggers SFW, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IEC (2010) Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. Am J Psychiatry 167:427–435.

Dierks T, Linden DE, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W (1999) Activation of Heschl's gyrus during auditory hallucinations. Neuron 22:615–621.

Eklund A, Nichols TE, Knutsson H (2016) Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Proc Natl Acad Sci U S A 113:7900–7905.

Esposito F, Scarabino T, Hyvarinen A, Himberg J, Formisano E, Comani S, Tedeschi G, Goebel R, Seifritz E, Di Salle F (2005) Independent component analysis of fMRI group studies by self-organizing clustering. NeuroImage 25:193–205.

Ey H (1973) Traité des hallucinations : tome 1. Paris: Masson. Available at: http://bsf.spp.asso.fr/index.php?lvl=notice_display&id=79490.

Ffytche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S (1998) The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat Neurosci 1:738–742.

Formisano E, Esposito F, Di Salle F, Goebel R (2004) Cortex-based independent component analysis of fMRI time series. Magn Reson Imaging 22:1493–1504.

Foucher JR (2013) Perspective in brain imaging and computer-assisted technologies for the treatment of hallucinations. In: The Neuroscience of Hallucinations. New York, NY: Springer New York. p 529–547.

Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15:870–878.

Hoffman RE, Fernandez T, Pittman B, Hampson M (2011): Elevated functional connectivity along a corticostriatal loop and the mechanism of auditory/verbal hallucinations in patients with schizophrenia. Biol Psychiatry 69:407–414.

Hor K, Taylor M (2010) Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol Oxf Engl 24:81–90.

Hyvärinen A, Oja E (2000) Independent component analysis: algorithms and applications. Neural Netw Off J Int Neural Netw Soc 13:411–430.

Jardri R, Pins D, Bubrovszky M, Lucas B, Lethuc V, Delmaire C, Vantyghem V, Despretz P, Thomas P (2009) Neural functional organization of hallucinations in schizophrenia: multisensory dissolution of pathological emergence in consciousness. Conscious Cogn 18:449–457.

Jardri R, Pins D, Delmaire C, Goeb J-L, Thomas P (2007) Activation of bilateral auditory cortex during verbal hallucinations in a child with schizophrenia. Mol Psychiatry 12:319.

Jardri R, Pouchet A, Pins D, Thomas P (2011) Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am J Psychiatry 168:73–81.

Jardri R, Thomas P, Delmaire C, Delion P, Pins D (2013) The neurodynamic organization of modality-dependent hallucinations. Cereb Cortex N Y N 1991 23:1108–1117.

Laird AR, Eickhoff SB, Li K, Robin DA, Glahn DC, Fox PT (2009) Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. J Neurosci Off J Soc Neurosci 29:14496–14505.

Lefebvre S, Demeulemeester M, Leroy A, Delmaire C, Lopes R, Pins D, Thomas P, Jardri R (2016) Network dynamics during the different stages of hallucinations in schizophrenia. Hum Brain Mapp 37:2571–2586.

Lennox BR, Park SB, Medley I, Morris PG, Jones PB (2000) The functional anatomy of auditory hallucinations in schizophrenia. Psychiatry Res 100:13–20.

Llorca PM, Pereira B, Jardri R, Chereau-Boudet I, Brousse G, Misdrahi D, Fénelon G, Tronche A-M, Schwan R, Lançon C, Marques A, Ulla M, Derost P, Debilly B, Durif F, de Chazeron I (2016) Hallucinations in schizophrenia and Parkinson's disease: an analysis of sensory modalities involved and the repercussion on patients. Sci Rep 6:38152.

Overgaard M, Fazekas P (2016) Can No-Report Paradigms Extract True Correlates of Consciousness? Trends Cogn Sci 20:241–242.

Roquet DR, Pham BT, Foucher JR (2014) Manual selection of spontaneous activity maps derived from independent component analysis: criteria and inter-rater reliability study. J Neurosci Methods 223:30-4.

Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK (2000) Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 57:1033–1038.

Shergill SS, Cameron LA, Brammer MJ, Williams SC, Murray RM, McGuire PK (2001) Modality specific neural correlates of auditory and somatic hallucinations. J Neurol Neurosurg Psychiatry 71:688–690.

Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootoonk S, Seaward J, McKenna P, Chua SE, Schnorr L (1995) A functional neuroanatomy of hallucinations in schizophrenia. Nature 378:176–179.

Slotema CW, Blom JD, de Weijer AD, Diederen KM, Goekoop R, Looijestijn J, Daalman K, Rijkaart A-M, Kahn RS, Hoek HW, Sommer IEC (2011) Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. Biol Psychiatry 69:450–456.

Sommer IEC, Diederen KMJ, Blom J-D, Willems A, Kushan L, Slotema K, Boks MPM, Daalman K, Hoek HW, Neggers SFW, Kahn RS (2008) Auditory verbal hallucinations predominantly activate the right inferior frontal area. Brain J Neurol 131:3169–3177.

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain, Thieme, New York.

Tan B-L (2009) Profile of cognitive problems in schizophrenia and implications for vocational functioning. Aust Occup Ther J 56:220–228.

Torgerson WS (1952) Multidimensional scaling: I. Theory and method. Psychometrika 17:401–419.

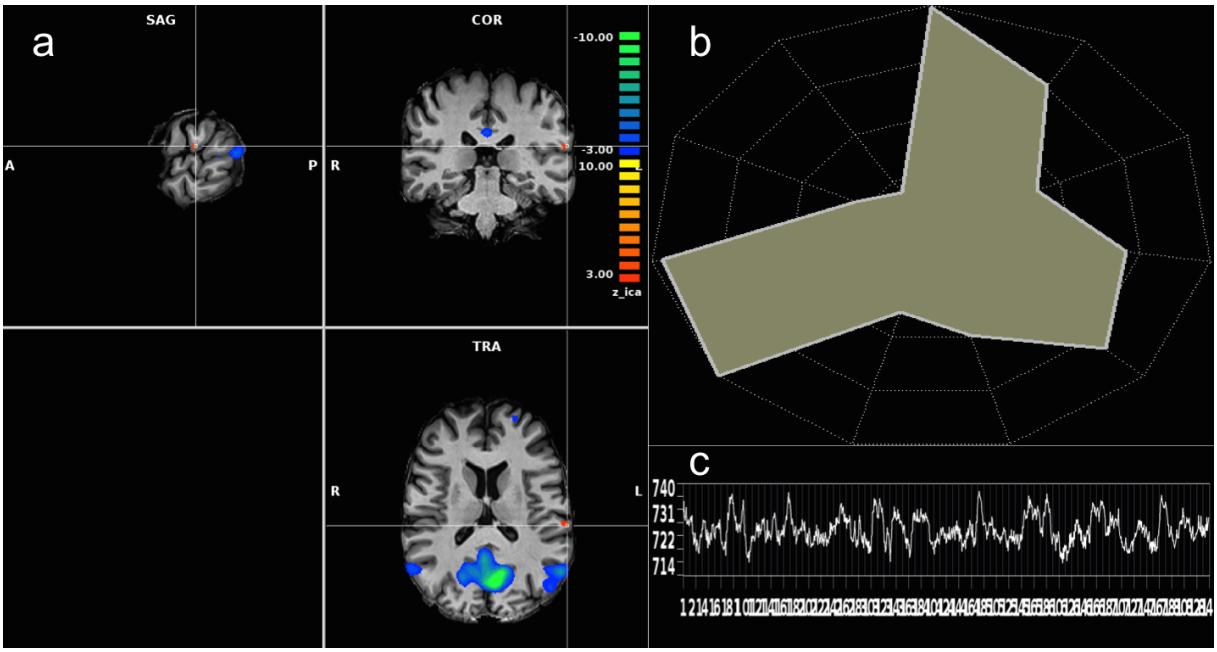
Tsuchiya N, Frässle S, Wilke M, Lamme V (2016) No-Report and Report-Based Paradigms Jointly Unravel the NCC: Response to Overgaard and Fazekas. Trends Cogn Sci 20:242–243.

Tsuchiya N, Wilke M, Frässle S, Lamme VAF (2015) No-Report Paradigms: Extracting the True Neural Correlates of Consciousness. Trends Cogn Sci 19:757–770.

van de Ven VG, Formisano E, Röder CH, Prvulovic D, Bittner RA, Dietz MG, Hubl D, Dierks T, Federspiel A, Esposito F, Di Salle F, Jansma B, Goebel R, Linden DEJ (2005) The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. NeuroImage 27:644–655.

van Lutterveld R, Diederen KMJ, Koops S, Begemann MJH, Sommer IEC (2013a) The influence of stimulus detection on activation patterns during auditory hallucinations. Schizophr Res 145:27–32.

Supplementary figure



Supplementary Figure 1: Example of ICA results at the subject-level. a) Selected Component of Interest in a patient experiencing auditory hallucinations while scanning (shown in the yellow-to-red color code). This cortical network appears negatively correlated with the Default-Mode Network (shown in the green-to-blue color code); **b)** Time course of the component of interest. Anatomo-functional data obtained in (a), as well as temporal dynamics obtained in (b), are compared with the post-fMRI interview of the participant; **c)** IC-fingerprint of the selected IC. Each axis of the polar plot corresponds to one of the normalized spatial, temporal or spectral parameters according to De Martino et al., 2007. In orange are the parameters associated with a neurophysiological source.

IV. Étude du rôle de l'insula antérieure dans l'amélioration des reviviscences post-traumatiques dans le TPST

Le TPST est un trouble qui peut se développer après exposition à un évènement traumatique impliquant un risque de décès ou de séquelles graves. En particulier, les reviviscences post-traumatiques sont un des symptômes cardinaux retrouvés dans le TPST. Nous savons que le SN joue un rôle important dans ces phénomènes intrusifs (McCurry et al., 2020). Néanmoins, la dynamique de ce réseau en cas de reviviscences, de même que l'influence de la réponse au traitement dans cette modulation fonctionnelle n'est pas totalement comprise à ce jour. Nous avons donc étudié la connectivité effective de l'insula antérieure bilatérale chez 30 patients issus d'un essai thérapeutique randomisé étudiant l'effet de la réactivation traumatique facilitée par propranolol, en utilisant la méthode du *Granger Causality Mapping*. Nous avons montré qu'une réponse positive au traitement sur les symptômes intrusifs était associée à une diminution de la connectivité de l'insula antérieure d'autant plus marquée que le score de sévérité diminuait. L'influence du réseau SN sur les régions limbiques, les régions impliquées dans la distinction soi-non soi et les régions impliquées dans le contrôle sensorimoteur, était diminuée chez les patients répondeurs versus les non-répondeurs. Par ailleurs, nous avons pu montrer que la sévérité des expériences intrusives était positivement corrélée avec la stabilité spatiale du DMN, mais négativement corrélée à la stabilité spatiale du CEN. Une étude ultérieure pourrait étudier la connectivité dynamique du réseau de saillance aux cours des différentes phases des reviviscences, à l'instar de ce que nous avons pu montrer dans les hallucinations.

ARTICLE 3

Intrusive experiences in post-traumatic stress disorder: treatment response induces changes in the effective connectivity of the anterior insula.

Leroy, A., Very, E., Birmes, P., Szaffarczyk, S., Lopes, R., Faure, C., Duhem, S., Grandgenèvre, P., Warembourg, F., Vaiva, G., & Jardri, R. (2020). Intrusive experiences in post-traumatic stress disorder: Treatment response induces changes in the effective connectivity of the anterior insula. *BioRxiv*.

INTRUSIVE EXPERIENCES IN POST-TRAUMATIC STRESS DISORDER: TREATMENT RESPONSE INDUCES CHANGES IN THE EFFECTIVE CONNECTIVITY OF THE ANTERIOR INSULA

Abbreviated title:

Insular Cortex Influence on Intrusivity

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ABSTRACT (251 words)

Introduction: One of the core features of posttraumatic stress disorder (PTSD) is reexperiencing the trauma. Th anterior insula (AI) was proposed to play a crucial role in these intrusive experiences. However, the dynamic function of the AI in reexperiencing trauma, as well as its putative modulation by effective therapy, still need to be specified.

Methods: Thirty PTSD patients were enrolled and exposed to chemo-facilitated traumatic memory reactivation therapy. Resting-state fMRI scans were acquired before and after treatment. To explore AI directed influences over the rest of the brain, we referred to a mixed-model using pre/post Granger causality analysis seeded on the AI as a within-subject factor and treatment response as a between-subject factor. To further identify correlates of reexperiencing trauma, we investigated how intrusive severity affected : (i) causality maps and (ii) the spatial stability of other intrinsic brain networks.

Results: We observed dynamic changes in AI effective connectivity in PTSD patients. Many within- and between-network causal paths were found to be less influenced by the AI after effective therapy. Insular influences were found positively correlated with flashback severity, while reexperiencing was linked with a stronger *default mode network* (DMN) and more unstable *central executive network* (CEN) connectivity.

Discussion: We showed that directed changes in AI signalling to the DMN and CEN at rest may underlie the degree of intrusive symptoms in PTSD. A positive response to treatment further induced changes in network-to-network anticorrelated patterns. Such findings may guide targeted neuromodulation strategies in PTSD patients not suitably improved by conventional treatment.

Key-words:

Post-Traumatic Stress Disorder; Propranolol; Therapeutics; salience network; fMRI

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a disabling condition that can be triggered by terrifying events that have the potential to disrupt life, such as interpersonal violence, combat, life-threatening accidents or disasters, as well as global pandemics (1). PTSD may lead to chronic psychiatric or addictive morbidities, loss of normal daily functioning, and increased risk of suicide (2). This disorder usually induces intrusive symptoms (i.e., distressing recollections of the event, including flashbacks and nightmares, often called "reexperiences"), persistent avoidance of stimuli associated with the trauma, negative alterations in cognitions or mood, and hyperarousal (3). "Reexperiencing" is considered central in the pathophysiology of PTSD, despite some similarities with other intrusive thoughts observed transdiagnostically, such as hallucinations, ruminations or persistent worries (4–7). Even if this research field is prolific, it still lacks a common neurofunctional signature for intrusive experiences that adequately circumscribes the underlying mechanisms of PTSD.

Brain-wide dysconnectivity has been suggested at the root of several psychiatric disorders, and key structures have picked the interest of PTSD scientists. Among the candidate nodes, the anterior insula (AI) was identified as one of the major connector hubs in the brain (8). This structure has been implicated in a large variety of functions, ranging from feelings representation to bodily and self-awareness (9). The AI receives convergent inputs from multiple sensory modalities, including the auditory and visual systems (10–14), and converging evidence supports its involvement in simultaneous attention to multisensory events (15,16). The AI was also proposed to tag salient endogenous and external information and further reallocate attentional resources towards them (17), making it a central element of the "salience network" (SN).

On a more pathological side, hyperarousal and re-experiencing were shown to be associated with increased activity in the bilateral AI and connected limbic structures, such as the amygdala (18) or the hippocampus (19). These symptoms were also associated with an increased functional connectivity of the SN network as a whole (20). Interestingly, aberrant SN effective connectivity was also proven involved in the process of switching from a state of unconstrained rest to one of experiencing hallucinatory events in schizophrenia patients (21), reinforcing the idea that this network may govern intrusive experiences in general.

In this vein, the SN is thought to tightly control the balance between various intrinsic networks and to swiftly move from rest to task-based actions and vice-versa, a theory that has been conceptualized as the tripartite model (17,22). According to this framework, the SN may drive commonly observed anticorrelated patterns between the default mode network (DMN, underlying self-referential processes) and the central executive network (CEN, involved in cognitive control and decision making), an interaction already shown to be impaired in PTSD. For instance, aberrant increases in SN and decreased DMN functional connectivity were described in PTSD patients (20), whereas a surge in connectivity strength of the CEN was reported to be associated with intrusiveness (23). Though these findings are encouraging, some gaps remain, such as the exact links between AI dysconnectivity and other biological theories of PTSD.

At the microscale level, we indeed know that SN activation is mediated by the B-noradrenergic system. In particular, activation of the locus coeruleus, the main source of epinephrine secretion in the brain, was found to be involved in SN activation (24). The administration of drugs increasing the epinephrine level has also been linked with SN activation (25,26), whereas the administration of propranolol, a noradrenergic beta-receptor

blocker, deactivates the SN (27). Finally, a genetic study revealed that only carriers of a common functional deletion in ADRA2B, a gene coding for the α2b-adrenoreceptor, displayed increased phasic amygdala responses under stress (28), again supporting the existence of an association between salience responses and B-noradrenergic regulation.

Interestingly, trauma memory reactivation therapy performed under the influence of propranolol (considered a putative reconsolidation blocker) was recently found to reduce symptom severity in PTSD (29). Referring to a similar randomized controlled trial (RCT) design, the present study intends to bring new insight to the dynamic role of the SN in PTSD and, more specifically, to circumscribe the directed influence of AI over the rest of the brain as a function of treatment response. We hypothesize that such chemo-facilitated treatment can modulate the effective connectivity of AI and that these plastic changes correlate with a reduction in trauma reexperiencing symptoms. In reference to the tripartite model, we also expect this downgrading in intrusiveness to be linked to changes in DMN and CEN spatial stability, demonstrating a brain-wide reallocation of cognitive resources in PTSD patients who respond to treatment.

MATERIALS AND METHODS

Population

Thirty patients with a primary diagnosis of PTSD according to DSM-IV-TR criteria (Structured Clinical Interview for DSM-IV, PTSD module) provided written informed consent to participate in the research (**Table 1**). They were all taken from a RCT testing for the efficacy of traumatic memory reactivation under the influence of propranolol versus placebo one week posttreatment. This trial received approval from an ethics committee (CPP 2009-012976-29) and was registered on clinicaltrials.gov (NCT01713556). The main results for this clinical trial are presented elsewhere (30).

Participants waiting for treatment were randomly and blindly allocated to two experimental groups (1:1 ratio): (i) a “propranolol” group, receiving traumatic memory reactivation + propranolol, and (ii) a “placebo” group, receiving traumatic memory reactivation + placebo. Propranolol or placebo was administered 90-minutes before a brief memory reactivation session, performed once a week for 6 consecutive weeks. The *Posttraumatic Stress Disorder Checklist Scale* - PCL-S (31) was used to quantify symptom severity and assess treatment response. Because we were interested in intrusive symptoms, we focused on the item sum of PCL-S Q1-to-Q5 (31). Assessment was made before treatment (V1) and one week after the end of the treatment (V7). The response to treatment was considered positive for at least a 30% decrease (32,33) in the PCL-S Q1-to-Q5 score compared to baseline.

MRI acquisition and data preprocessing

Patients underwent two MRI sessions at rest with their eyes closed (at V1 and V7) on a 3T Philips Achieva scanner with an 8-channel head coil. Each of these sessions included a 4-min T1-weighted (T1w) 3D anatomical run (124 transverse slices, field of view = 256 mm^3, vox = 0.8 mm^3) and a 15-min T2*-weighted 3D-PRESTO sequence (34–36). This functional sequence (dynamic scan time = 1000 ms, TE = 9.6 ms, flip angle = 9°, vox = 3.3 mm^3) allowed for full functional brain coverage with a temporal resolution particularly suited for effective connectivity analysis (37).

Anatomical and functional MRI data were preprocessed using the FMRIPrep pipeline v. 1.5 (38), a Nipype v. 1.2.2 based tool (39). T1w images were corrected for nonuniform intensity and skull stripped. Brain tissue segmentation of cerebrospinal fluid, white-matter and gray-matter was performed on the brain-extracted T1w image. Volume-based spatial normalization to the *Montreal Neurological Institute* ICBM-152 (MNI) template was performed through nonlinear registration using brain-extracted versions of both the T1w reference and the MNI template.

For functional images, a reference BOLD volume and its skull-stripped version were generated and coregistered to the T1w image using a boundary-based registration algorithm with 9 degrees of freedom. Head-motion parameters were estimated before spatiotemporal filtering. Motion correction, BOLD-to-T1w transformation and T1w-to-template (MNI) warps were concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0) based on Lanczos interpolation. Spatial smoothing with a 6-mm isotropic Gaussian kernel was then performed, and a second "nonaggressive" denoising step was conducted using

independent component analysis [ICA-AROMA]. Linear trends were finally removed, and a high-pass temporal filtering with 3 cycles/point was applied.

Granger causality analysis

Effective connectivity was assessed using Granger causality analysis (GCA), which allows for the data-driven exploration of a reference region's influence over the brain as well as targets of influence on the same given area (40). We used this approach to account for the multiple regions naturally connected to the SN (41) and to avoid missing brain areas that could not have been retained in a more traditional theory-driven framework. Here, we used the implementation proposed in the BrainVoyager software suite (v21.4, BrainInnovation, Maastricht; *Granger Causality Mapping* plugin v1.5). We defined the bilateral AI, according to the meta-analysis from Laird et al. (**Figure 1**) (2011) (42) , as the reference region for later analyses. GCA maps were used to visualize the directed influences between the AI and every voxel in both directions after applying a gray-matter mask. These maps were thresholded using a false-discovery rate approach at q-levels of 0.01. We finally tested the association between GCA maps and symptom severity at the V7 time-point, considering $p_{fwe}<0.05$ as significant.

Main statistical analysis

To assess changes in AI effective-connectivity pre/post treatment between patients who respond to treatment (responders) and those who did not (nonresponders), we referred to a 2x2 mixed-model ANOVA, using GCA maps at V1 and V7 as within-subject factors and treatment response as a between-subject factor. Post-hoc analyses used Student's t-tests. All maps were then thresholded using a cluster-based permutation method

(43). To prevent potential inflated false-positive rates (44), we first specified a cluster-defining threshold (CDT) at $p_{uncorrected} < 0.001$. After conducting a 1000-iteration Monte-Carlo simulation, a cluster-extent threshold was defined as a value high enough to keep the family-wise error at $p_{fwe}=0.05$. The resulting brain areas were labeled using the Anatomy toolbox v 3.0 (https://github.com/inm7/jubrain-anatomy-toolbox, (45)).

Intrinsic network spatial stability measure

In parallel, we also explored the spatial stability of the DMN and the CEN posttreatment (i.e., the V7 time-point) using a "goodness-of-fit" (GoF) procedure. After decomposing each posttreatment functional dataset using *independent component analysis* (ICA), we selected the components exhibiting the highest spatial correlation with an a priori template. For each participant, this procedure was repeated twice : with the DMN and the CEN template, respectively (46). The resulting GoF scores were assumed to reflect posttreatment DMN and CEN spatial stability. We tested for an association between these scores and the severity of intrusive symptoms using Pearson's *r* correlation test, considering $p<0.05$ as significant.

RESULTS

Demographic and clinical variables

At baseline, responders and nonresponders were comparable in terms of (i) sociodemographic characteristics (age and sex-ratio), and (ii) symptom severity (PCL-S scores/subscores and depressive symptoms measured with the *Beck Depression Inventory* (47)). Note that, counterintuitively, the responder group contained fewer patients receiving propranolol (see (30) for a more detailed description of the RCT main findings).

Table 1. Population description

	Responders (n=16)	**Nonresponders (n = 14)**
Age	41.3 (12.3)	36.6 (13.5)
Sex (Male /Female)	7/9	8/6
Dvars	24.3 (3.74)	24.1 (4.05)
Global signal	887 (121)	916 (96.3)
Total PCL-S score	65.4 (9.34)	68.4 (9.34)
PCLS-score (question 1 to 5)	18.9 (3.38)	19.4 (3.38)
Beck Depression inventory score	25.9 (14.5)	28.9 (11.3)
*Rate of patients receiving propranolol **	*31.3 %*	*78.6%*

*p <0.05.

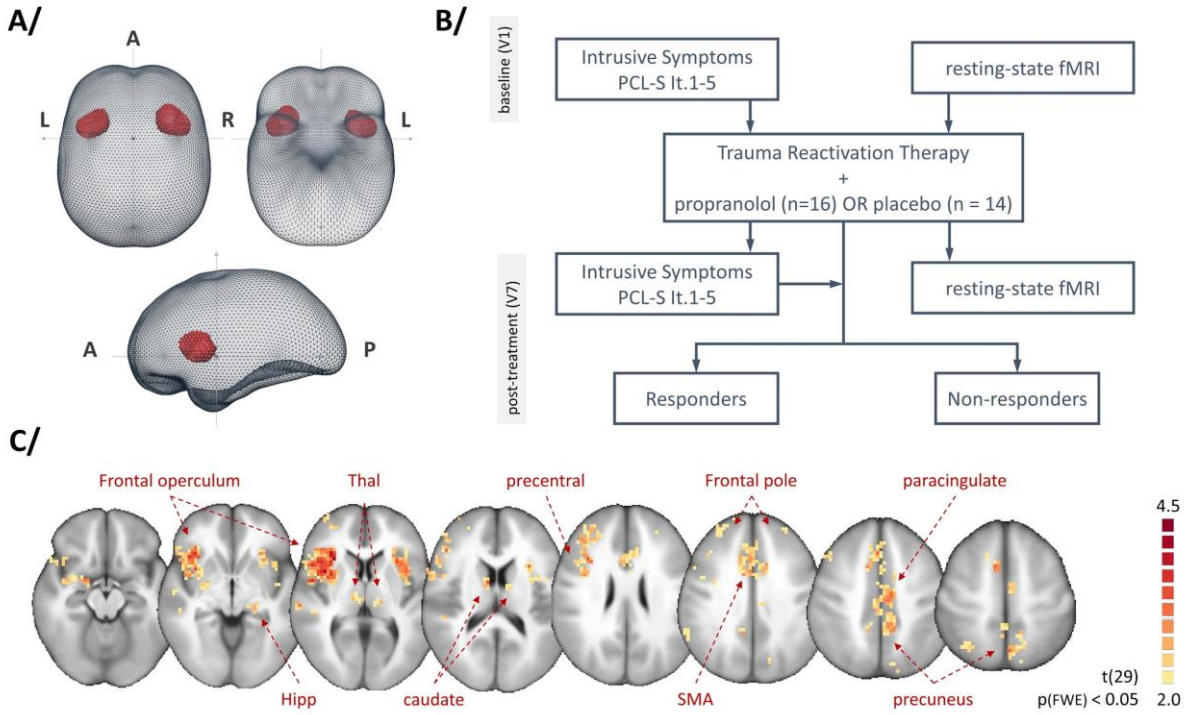


Figure 1. **Study design and *Granger causality analysis* (GCA) seeded on the anterior insula in PTSD patients. (A)** The bilateral anterior insula was chosen as the region of interest for GCA and is presented in red in a glass brain. **(B)** Flow chart of the study. We defined responders as patients with at least a 30% decrease in PCL-S scores at V7 compared with baseline (V1). **(C)** Whole-sample random-effects GCA map at V1. PCL-S: Posttraumatic Stress Disorder Checklist Scale; Thal: thalamus; Hipp: hippocampus; SMA: supplementary motor area; A: anterior; P: posterior; L/R: left/right sides of the brain.

AI effective connectivity at V1

GCA performed on the whole-sample at baseline revealed that the bilateral AI significantly modulates a group of regions involved in motor preparation, execution and action monitoring (i.e., precentral gyrus, the supplementary motor area, the left thalamus, and the frontal pole), as well as in visuospatial processing (i.e., the paracingulate gyrus and the precuneus). See **Figure 1** and **Suppl. Table 1**. No specific connectivity differences were evidenced between the responder and nonresponder groups before treatment.

AI effective-connectivity changes between V1 and V7

The mixed-model ANOVA revealed significant changes in AI causal maps after treatment. A significant [time-point x group] interaction was evidenced: (i) laterally, in the mid- and posterior insula, amygdala, precentral gyrus and supramarginal gyrus ; and (ii) medially, in the cingulate cortex (anterior and posterior) and the precuneus (**Suppl. Table 2**). Compared with nonresponders, patients showing clinical improvement exhibited a reduced influence of the AI over a wide socioemotional network composed of the superior frontal gyrus, anterior and posterior supramarginal gyri, anterior and posterior cingulate, central operculum and right amygdala. Conversely, responders exhibited a higher influence of the AI over the precuneus (Cf. **Figure 2**, **Table 2**). Simple pre/posttreatment contrasts for responders and nonresponders are available in **Suppl. Figures 1, 2** and **Suppl. Tables 3, 4** respectively, whereas significant results for propranolol vs placebo at V7 are presented in **Suppl. Table 5**.

Regression analysis conducted posttreatment further revealed that the more severe the intrusive symptoms were, the greater the AI exerted influence over somatosensory and motor regions (i.e., the posterior insula, right parietal operculum, and precentral gyrus), as

well as over brain areas involved in visuospatial processing (the paracingulate gyrus) and self-other processing (i.e., the anterior and posterior cingulate cortices, superior frontal gyrus and supramarginal gyrus). See **Figure 3**.

Table 2. Changes in the anterior insula effective connectivity between responder and nonresponder patients. Regions exhibiting a significant difference in *Granger causality analysis* maps between V1 and V7 according to treatment response. Coordinates are reported in MNI (Montreal Neurological Institute) space.

x	y	z	t	p	Label
-63	-45	36	-3.813837	0.000662	Left Supramarginal Gyrus. posterior division
-57	-30	39	-4.072859	0.000328	Left Supramarginal Gyrus. anterior division
-6	-39	45	-3.452251	0.001728	Cingulate Gyrus. posterior division
-3	30	27	-2.993126	0.005594	Cingulate Gyrus. anterior division
6	-72	42	3.098338	0.004296	Right Precuneus Cortex
21	-9	66	-3.458369	0.0017	Superior Frontal Gyrus
27	3	-12	-2.894758	0.007138	Right amygdala
45	0	9	-2.875736	0.007479	Right Central Opercular Cortex

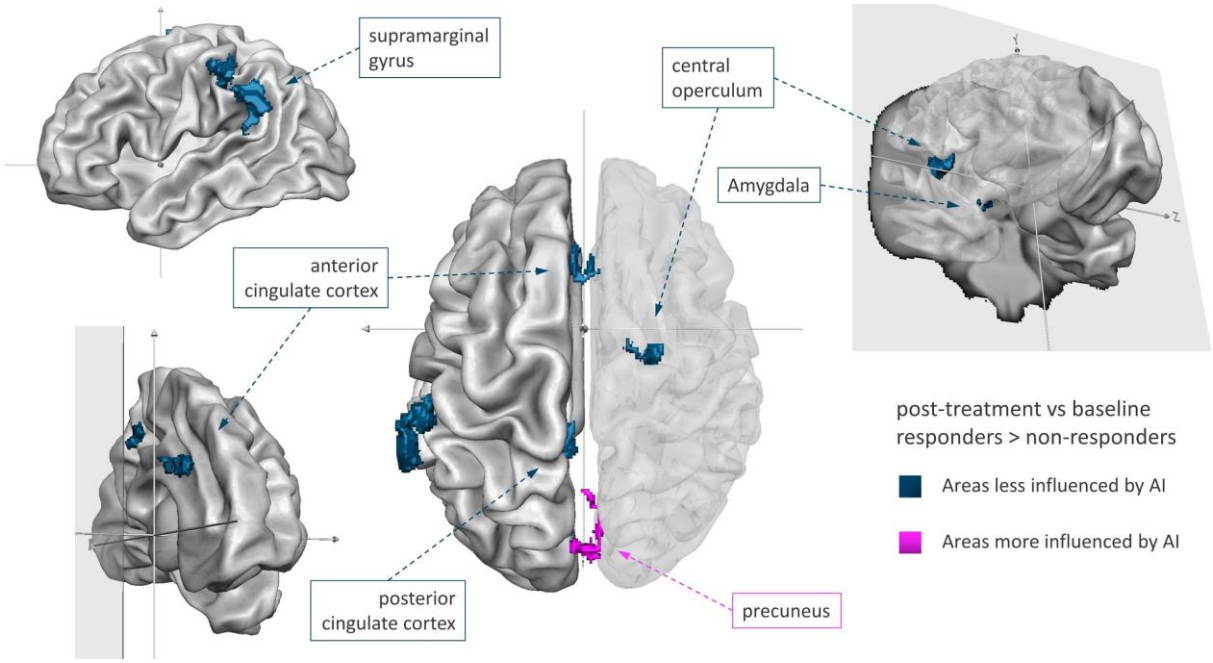


Figure 2. Changes in *Granger causality* maps seeded on the anterior insula (AI) between responders and nonresponders to chemo-facilitated therapy in PTSD. We used a transparent right hemisphere to allow visualization of the deeper clusters. Brain areas less influenced by AI after effective treatment are depicted in dark blue. The precuneus (pink) was the only cluster found to be more influenced by AI posttreatment in responders than in nonresponders.

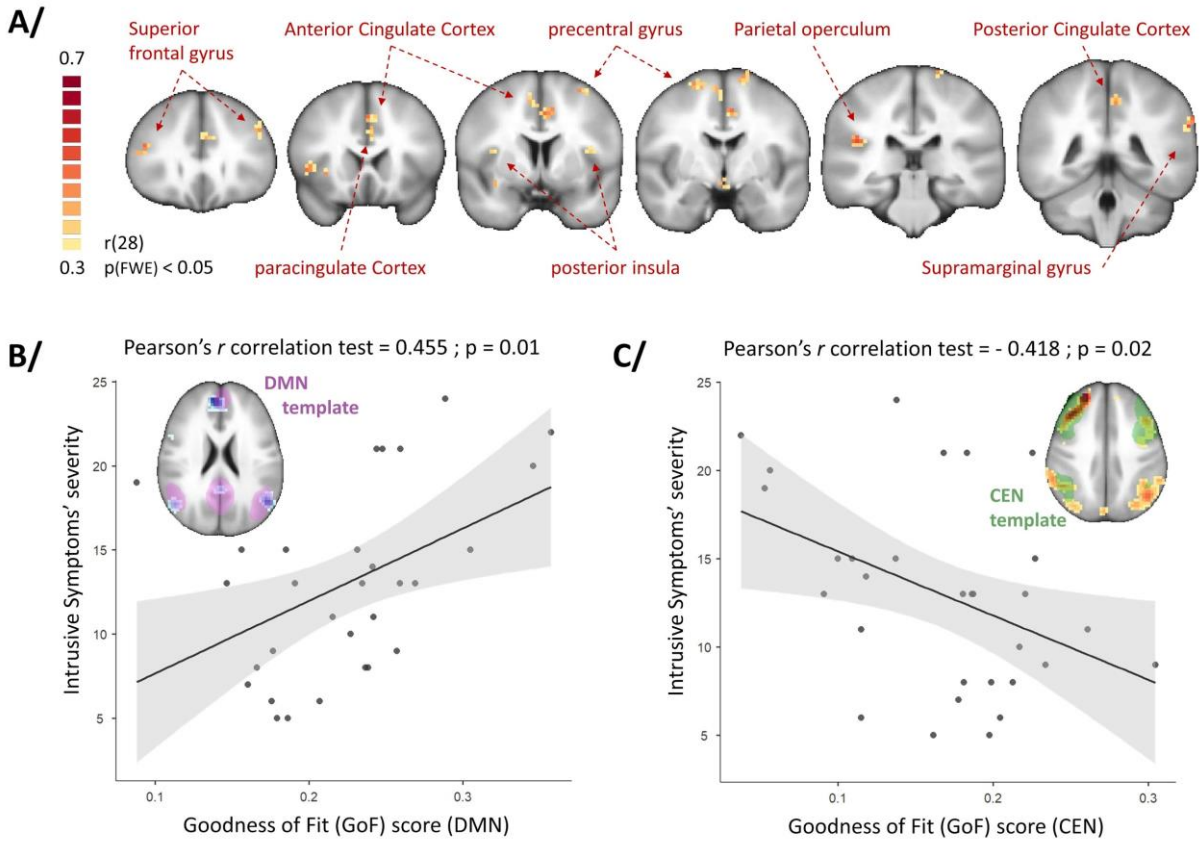


Figure 3. Brain correlates of intrusive symptom severity in PTSD. **(A)** Linear regression analysis showing the brain regions exhibiting a positive association between the severity of intrusive symptoms and thresholded *Granger causality analysis* maps at V7. **(B, C)** Correlation analyses between intrinsic network stability and the severity of intrusive symptoms at V7. A positive association was indicated by the default mode network stability (DMN GoF score), shown in **(B)**, whereas a negative association was indicated by the central executive network stability (CEN GoF score), shown in **(C)**.

Intrinsic network spatial stability measure at V7

Finally, the assessment of the spatial stability of the DMN and CEN posttreatment revealed that the severity of “reexperiencing” symptoms was positively correlated with the DMN GoF scores (**r = 0.521, p = 0.003**) and negatively correlated with the CEN GoF scores (**r = -0.418 p = 0.021** - Cf. **Figure 3**).

DISCUSSION

The present fMRI study was designed to explore how an effective chemo-facilitated psychotherapy for intrusive symptoms in PTSD could modulate AI causal influences over the brain. Very limited fMRI studies measured pre/post treatment changes in PTSD (48) and to our knowledge, none of them included effective connectivity. We focused on the AI since this region is known to be: (i) a central integration hub serving sensory, emotional, motivational and cognitive functions, (ii) under B-noradrenergic regulation, and (iii) potentially involved in re-experiencing trauma. Using high temporal-resolution fMRI and comparing pre/post therapy GCA results in PTSD patients, we were able to provide evidence that treatment response was associated with a significant reduction in AI effective connectivity towards motor and socioaffective regions, a global decrease that follows symptom severity reduction.

The first set of regions modulated by AI corresponded to limbic areas for which dense reciprocal connections with the ventral AI were repeatedly described. A strong body of evidence supports AI mediation in fear and anxiety, which was regularly found to be coactivated with the amygdala in stressful contexts (9). By showing a reduced influence of AI on the amygdala in responders compared with nonresponders, we can assume that one of the first effects of treatment was to temper the emotional storm associated with reexperiencing and hyperarousal (18). This finding nicely complements the existing literature in which joint amygdalar and insular overactivation is described in the context of PTSD (20) and declines after successful psychotherapy (49). The ability to better modulate AI connectivity following therapy could be associated with better cross-talk between untargeted inner thoughts and the ability to focus attention on stimulus-dependent demands (50), a theory also supported by the association found between symptom severity

and AI influence over visuospatial areas. Using GCA, we were able to attest that AI primarily drives this pathological interaction in PTSD.

The second set of brain areas modulated by AI are involved in self-other distinction and may support dissociative experiences frequently observed in PTSD. This is the case for the precuneus, frontal superior and supramarginal gyri, all regularly found to be involved in self-awareness and agency processing (e.g., (51)). These cognitive functions are more usually under the influence of the dorsal AI (52). Interestingly, localized AI lesions can induce dissociative experiences, such as the (rare) “pain asymbolia” syndrome, in which pain recognition appears disconnected from its appropriate emotional response (9). Within this functional network, the supramarginal gyrus, located at the temporo-parietal junction, has also been linked with experiences involving a sensorial component. Similar to the AI, the supramarginal gyrus receives heavy sensory inputs ranging from the auditory to the somatosensory modality. The crossmodal nature of this area makes it particularly well suited for linking sensory experiences with cognitive and/or affective information. Finally, the supramarginal gyrus is also involved in the phonological and articulatory processing of words (53), making it solicistable by talking therapy. Again, this is perfectly in line with the present findings showing that the AI influence on this network was correlated with the degree of intrusion and was significantly decreased in facilitated psychotherapy responders.

The third set of regions influenced by AI is engaged in sensorimotor control (54–56) and might be involved in the autonomic and behavioral responses to stress. Again, this interaction was found to correlate with symptom severity, even if only indirectly through the posterior insula and thalamic relays (57), which were found to be under AI control at baseline. The motor network under consideration includes the caudal anterior cingulate

cortex (cACC), the supplementary motor area and the precentral gyrus. A decreased resting-state functional connectivity between the cACC and the precentral gyrus was previously evidenced in veterans with or without PTSD compared to healthy controls, suggesting that military training or deployment, including trauma exposure, may influence SN connectivity (58). In addition, precentral activity has been related to defensive behaviors in animals (59) and may subserve the increased "fight or flight" response regularly observed in PTSD when facing mental stress.

In addition to networks sustaining the rich phenomenology of PTSD symptoms, we also investigated how effective treatment may dynamically affect the interaction between intrinsic neural networks. We first demonstrated that the more the AI exerted a causal influence over core nodes of the DMN (such as the rostral ACC, the posterior cingulate and the precuneus), the more severe intrusive symptoms were, and that this interaction differentially changed at V7 according to the treatment response. This finding appears in line with previous studies conducted in schizophrenia patients (21), showing that increased control from the SN to the DMN initiates hallucinatory states. Interestingly, the DMN is also known to anti-correlate with task-related networks, such as the CEN (60,61), and this antagonistic activity was proposed to be tuned by the AI (22). Returning to our schizophrenia example, a CEN takeover was found to drive the extinction of hallucinations (21). Here, we found that reexperiencing the trauma positively correlated with DMN stability and presented a reversed pattern for the CEN. Altogether, these results support the idea that intrusive symptoms could correspond to self-referential mental activities driven by impaired AI control over the DMN/CEN balance, making salient memory fragments active enough (through bottom-up amplification) to aberrantly intrude into consciousness.

Despite these encouraging findings, some issues need to be further discussed. If the abovementioned theory is correct, we could expect to find the hippocampal complex among the regions influenced by the AI. The limited sample-size of the present trial may account for such a negative result (i.e., a power issue), and the exact relationship between the AI and this limbic structure will have to be clarified in future studies. In fact, several brain areas identified in this study have previously been shown to be involved in memory suppression beyond the medial temporal lobe. This is the case for the precuneus and the frontal cortex (62), which have tight connections with the hippocampus (63,64). The same is true for other limbic structures, such as the amygdala which have strong reciprocal connections with the hippocampus. We cannot exclude that intermediate small brain structures, such as the hippocampus, that are involved in a chain of causality could be more vulnerable and may not survive statistical thresholding. Based on that possibility, we hypothesize a triple interaction [AI - amygdala - hippocampus] at the root of the memorization of trauma-related emotional valence, constituting an interesting complementary track for future research on PTSD.

A second potential issue resides in the fact that GCA indicates the dominant direction of influence, introducing ambiguity in the interpretation of pre/post treatment contrast maps, as they may potentially result from a decrease in the influence of AI-to-target-regions influence or from an increase in the influence of target-to-AI. This problem can, for instance, be illustrated by considering a recent study of effective connectivity in PTSD that reached seemingly opposite conclusions, suggesting that frontal regions exerted a reduced influence on AI (65). In the same vein, a decreased causal flow from the right amygdala to the right insula in PTSD patients relative to trauma-exposed controls has been suggested (23), which again appears in apparent contradiction with the present findings. Even if the samples and designs were not exactly comparable, methodological advances should help to reconcile

these findings, but until then, this literature needs to be interpreted with caution and in reference to clinically and anatomo-functionally available knowledge at the time of publication.

A final point we would like to insist on is that we focused on symptom reduction, regardless of the initial group of randomisation in the *Pre-Reactivation Propranolol Therapy* trial. Of course, the full results of the RCT have been presented elsewhere (30) and are beyond the scope of the present paper. Note that the between-group differences were both explained by changes in the responder and nonresponder groups. This is compatible with previous studies showing that psychotherapy could induce functional changes, even in cases of no clinical response (48), that could be linked with repeated trauma exposure without extinction, as suggested in previous studies (58). Importantly, because half of the sample did not reach the threshold for a positive response to chemo-facilitated psychotherapy, we expect our findings to also be relevant for future neuromodulation trials for severely impaired PTSD patients. In this vein, a recent study confirmed that such patients could be trained to downregulate amygdalar activity using real time fMRI-based neurofeedback (66).

Overall, we were able to provide experimental support for the causal role played by AI in reexperiencing trauma. Notably, we showed that effective facilitated psychotherapy was linked with plastic changes in AI directed influence over sensorimotor, cognitive and socioemotional networks. Dynamically, restoration of the DMN-to-CEN switch control was also observed, offering an attractive mechanism for intrusion. We hope that the present results will contribute to paving the way for new evidenced-based treatments of intrusive symptoms in PTSD, considering AI as a particularly interesting target for this purpose.

REFERENCES:

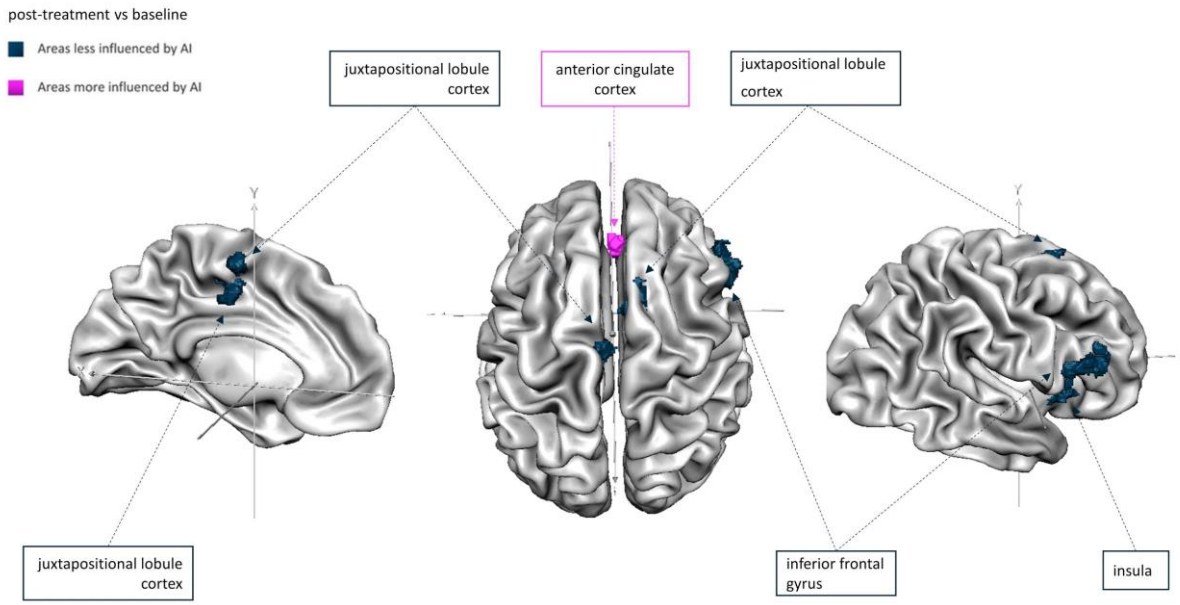
1. Horesh D, Brown AD (2020): Traumatic stress in the age of COVID-19: A call to close critical gaps and adapt to new realities. *Psychol Trauma Theory Res Pract Policy* 12: 331–335.
2. Lewis SJ, Arseneault L, Caspi A, Fisher HL, Matthews T, Moffitt TE, *et al.* (2019): The epidemiology of trauma and post-traumatic stress disorder in a representative cohort of young people in England and Wales. *Lancet Psychiatry* 6: 247–256.
3. American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596
4. Brewin CR, Gregory JD, Lipton M, Burgess N (2010): Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. *Psychol Rev* 117: 210–232.
5. Larøi F, Sommer IE, Blom JD, Fernyhough C, Ffytche DH, Hugdahl K, *et al.* (2012): The characteristic features of auditory verbal hallucinations in clinical and nonclinical groups: state-of-the-art overview and future directions. *Schizophr Bull* 38: 724–733.
6. Newman MG, Llera SJ, Erickson TM, Przeworski A, Castonguay LG (2013): Worry and generalized anxiety disorder: a review and theoretical synthesis of evidence on nature, etiology, mechanisms, and treatment. *Annu Rev Clin Psychol* 9: 275–297.
7. Watkins ER (2008): Constructive and unconstructive repetitive thought. *Psychol Bull* 134: 163–206.
8. van den Heuvel MP, Sporns O (2013): Network hubs in the human brain. *Trends Cogn Sci* 17: 683–696.
9. Gogolla N (2017): The insular cortex. *Curr Biol CB* 27: R580–R586.
10. Augustine JR (1996): Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Rev* 22: 229–244.
11. Bamiou D-E, Musiek FE, Luxon LM (2003): The insula (Island of Reil) and its role in auditory processing: Literature review. *Brain Res Rev* 42: 143–154.
12. Butti C, Hof PR (2010): The insular cortex: a comparative perspective. *Brain Struct Funct* 214: 477–493.
13. Mesulam M-M, Mufson EJ (1982): Insula of the old world monkey. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *J Comp Neurol* 212: 1–22.
14. Nieuwenhuys R (2012): Chapter 7 - The insular cortex: A review. In: Hofman MA, Falk D, editors. *Progress in Brain Research*, vol. 195. Elsevier, pp 123–163.
15. Bushara, Grafman J, Hallett M (2001): Neural correlates of auditory-visual stimulus onset asynchrony detection. *J Neurosci Off J Soc Neurosci* 21: 300–304.
16. Bushara, Hanakawa T, Immisch I, Toma K, Kansaku K, Hallett M (2003): Neural correlates of cross-modal binding. *Nat Neurosci* 6: 190–195.
17. Menon, Uddin LQ (2010): Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct* 214: 655–667.
18. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, *et al.* (2015): Post-traumatic stress disorder. *Nat Rev Dis Primer* 1: 15057.
19. Stevens JS, Reddy R, Kim YJ, van Rooij SJH, Ely TD, Hamann S, *et al.* (2018): Episodic memory after trauma exposure: Medial temporal lobe function is positively related to re-experiencing and inversely related to negative affect symptoms. *NeuroImage Clin* 17: 650–658.
20. Koch SBJ, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M (2016): Aberrant resting-

state brain activity in posttraumatic stress disorder: a meta-analysis and systematic review. *Depress Anxiety* 33: 592–605.
21. Lefebvre S, Demeulemeester M, Leroy A, Delmaire C, Lopes R, Pins D, *et al.* (2016): Network dynamics during the different stages of hallucinations in schizophrenia. *Hum Brain Mapp* 37: 2571–2586.
22. Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A* 105: 12569–12574.
23. Weng Y, Qi R, Zhang L, Luo Y, Ke J, Xu Q, *et al.* (2019): Disturbed effective connectivity patterns in an intrinsic triple network model are associated with posttraumatic stress disorder. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol* 40: 339–349.
24. Zerbi V, Floriou-Servou A, Markicevic M, Vermeiren Y, Sturman O, Privitera M, *et al.* (2019): Rapid Reconfiguration of the Functional Connectome after Chemogenetic Locus Coeruleus Activation. *Neuron* 103: 702-718.e5.
25. Onur OA, Walter H, Schlaepfer TE, Rehme AK, Schmidt C, Keysers C, *et al.* (2009): Noradrenergic enhancement of amygdala responses to fear. *Soc Cogn Affect Neurosci* 4: 119–126.
26. Cameron OG, Minoshima S (2002): Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. *Psychosom Med* 64: 851–861.
27. Hermans EJ, van Marle HJF, Ossewaarde L, Henckens MJAG, Qin S, van Kesteren MTR, *et al.* (2011): Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science* 334: 1151–1153.
28. Cousijn H, Rijpkema M, Qin S, van Marle HJF, Franke B, Hermans EJ, *et al.* (2010): Acute stress modulates genotype effects on amygdala processing in humans. *Proc Natl Acad Sci U S A* 107: 9867–9872.
29. Brunet A, Saumier D, Liu A, Streiner DL, Tremblay J, Pitman RK (2018): Reduction of PTSD Symptoms With Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial. *Am J Psychiatry* 175: 427–433.
30. Roullet P, Vaiva G, Véry E, Bourcier A, Yrondi A, Dupuch L, *et al.* (submitted): Traumatic memory reactivation with or without propranolol for PTSD and comorbid MD symptoms: A randomized clinical trial.
31. Ventureyra VAG, Yao S-N, Cottraux J, Note I, De Mey-Guillard C (2002): The validation of the Posttraumatic Stress Disorder Checklist Scale in posttraumatic stress disorder and nonclinical subjects. *Psychother Psychosom* 71: 47–53.
32. Brady F, Warnock-Parkes E, Barker C, Ehlers A (2015): Early in-session predictors of response to trauma-focused cognitive therapy for posttraumatic stress disorder. *Behav Res Ther* 75: 40–47.
33. Mushtaq D, Ali A, Margoob MA, Murtaza I, Andrade C (2012): Association between serotonin transporter gene promoter-region polymorphism and 4- and 12-week treatment response to sertraline in posttraumatic stress disorder. *J Affect Disord* 136: 955–962.
34. Liu G, Sobering G, Duyn J, Moonen CT (1993): A functional MRI technique combining principles of echo-shifting with a train of observations (PRESTO). *Magn Reson Med* 30: 764–768.
35. Neggers SFW, Hermans EJ, Ramsey NF (2008): Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-

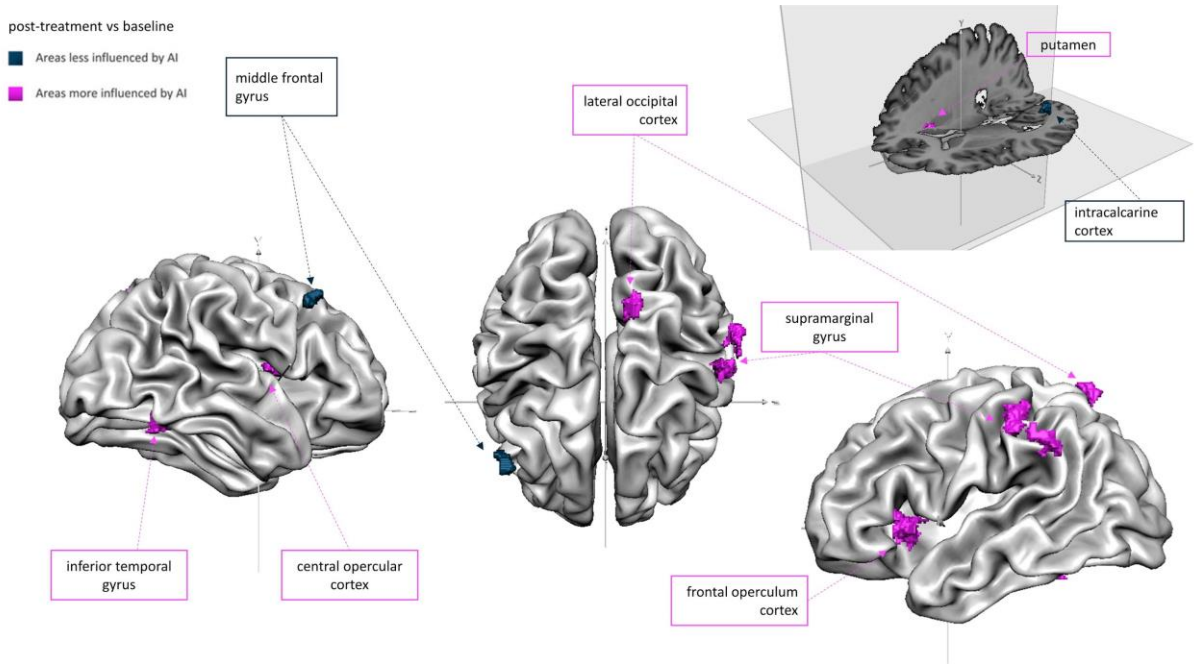
PRESTO and 2D-EPI at 3 T. *NMR Biomed* 21: 663–676.
36. van Gelderen P, Duyn JH, Ramsey NF, Liu G, Moonen CTW (2012): The PRESTO technique for fMRI. *NeuroImage* 62: 676–681.
37. Deshpande G, Hu X (2012): Investigating effective brain connectivity from fMRI data: past findings and current issues with reference to Granger causality analysis. *Brain Connect* 2: 235–245.
38. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, *et al.* (2019): fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods* 16: 111–116.
39. Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, Ghosh SS (2011): Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. *Front Neuroinformatics* 5: 13.
40. Roebroeck A, Formisano E, Goebel R (2005): Mapping directed influence over the brain using Granger causality and fMRI. *NeuroImage* 25: 230–242.
41. Menon (2015): Salience Network. In: Toga AW, editor. *Brain Mapping*. Waltham: Academic Press, pp 597–611.
42. Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, *et al.* (2011): Behavioral interpretations of intrinsic connectivity networks. *J Cogn Neurosci* 23: 4022–4037.
43. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 33: 636–647.
44. Eklund A, Nichols TE, Knutsson H (2016): Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A* 113: 7900–7905.
45. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005): A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage* 25: 1325–1335.
46. Greicius MD, Srivastava G, Reiss AL, Menon V (2004): Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A* 101: 4637–4642.
47. Beck AT, Steer RA, Carbin MG (1988): Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev* 8: 77–100.
48. Simmons AN, Norman SB, Spadoni AD, Strigo IA (2013): Neurosubstrates of remission following prolonged exposure therapy in veterans with posttraumatic stress disorder. *Psychother Psychosom* 82: 382–389.
49. Malejko K, Abler B, Plener PL, Straub J (2017): Neural Correlates of Psychotherapeutic Treatment of Post-traumatic Stress Disorder: A Systematic Literature Review. *Front Psychiatry* 8: 85.
50. Szeszko PR, Yehuda R (2019): Magnetic resonance imaging predictors of psychotherapy treatment response in post-traumatic stress disorder: A role for the salience network. *Psychiatry Res* 277: 52–57.
51. Sperduti M, Delaveau P, Fossati P, Nadel J (2011): Different brain structures related to self- and external-agency attribution: a brief review and meta-analysis. *Brain Struct Funct* 216: 151–157.
52. Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB (2010): A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct* 214: 519–534.
53. Stoeckel C, Gough PM, Watkins KE, Devlin JT (2009): Supramarginal gyrus involvement in

visual word recognition. *Cortex J Devoted Study Nerv Syst Behav* 45: 1091–1096.
54. Chouinard PA, Paus T (2006): The primary motor and premotor areas of the human cerebral cortex. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry* 12: 143–152.
55. Dum RP, Strick PL (1991): The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci Off J Soc Neurosci* 11: 667–689.
56. Paus T (2001): Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci* 2: 417–424.
57. Uddin LQ, Nomi JS, Hebert-Seropian B, Ghaziri J, Boucher O (2017): Structure and function of the human insula. *J Clin Neurophysiol Off Publ Am Electroencephalogr Soc* 34: 300.
58. Kennis M, Rademaker AR, van Rooij SJH, Kahn RS, Geuze E (2014): Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. *Hum Brain Mapp* 36: 99–109.
59. Graziano MSA, Cooke DF (2006): Parieto-frontal interactions, personal space, and defensive behavior. *Neuropsychologia* 44: 845–859.
60. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102: 9673–9678.
61. Greicius MD, Krasnow B, Reiss AL, Menon V (2003): Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100: 253–258.
62. Mary A, Dayan J, Leone G, Postel C, Fraisse F, Malle C, *et al.* (2020): Resilience after trauma: The role of memory suppression. *Science* 367. https://doi.org/10.1126/science.aay8477
63. Cunningham SI, Tomasi D, Volkow ND (2017): Structural and functional connectivity of the precuneus and thalamus to the default mode network. *Hum Brain Mapp* 38: 938–956.
64. Anderson MC, Bunce JG, Barbas H (2016): Prefrontal-hippocampal pathways underlying inhibitory control over memory. *Neurobiol Learn Mem* 134 Pt A: 145–161.
65. Rangaprakash D, Dretsch MN, Venkataraman A, Katz JS, Denney TS, Deshpande G (2018): Identifying disease foci from static and dynamic effective connectivity networks: Illustration in soldiers with trauma. *Hum Brain Mapp* 39: 264–287.
66. de Pierrefeu A, Fovet T, Hadj-Selem F, Löfstedt T, Ciuciu P, Lefebvre S, *et al.* (2018): Prediction of activation patterns preceding hallucinations in patients with schizophrenia using machine learning with structured sparsity. *Hum Brain Mapp* 39: 1777–1788.

SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Changes in *Granger causality* maps seeded on the anterior insula (AI) in responders to chemo-facilitated therapy in PTSD (cortical clusters). Brain areas less influenced by AI after effective treatment are depicted in dark blue. Brain areas more influenced by AI after effective treatment are depicted in pink (i.e. dorsal anterior cingulate cortex, part of the salience network).



Supplementary Figure 2. Changes in *Granger Causality* maps seeded on the Anterior Insula (AI) in non-responders to chemo-facilitated therapy in PTSD (cortical clusters). Brain areas less influenced by AI after effective treatment are depicted in dark blue. Brain areas more influenced by AI after effective treatment are depicted in pink.

Supplementary table 1. Whole-sample *Granger causality analysis* seeded on the anterior insula at baseline. Coordinates are reported in MNI (Montreal Neurological Institute) space.

x	y	z	GCM score	p	label
42	9	3	2.343144	0.000034	Central Opercular Cortex
36	18	27	1.625094	0.001433	Middle Frontal Gyrus
27	-33	69	1.081782	0.008486	Postcentral Gyrus
-3	-15	48	1.625094	0.000595	Precentral Gyrus
9	-48	36	2.054894	0.007480	Cingulate Gyrus, posterior division
-6	-60	54	0.781360	0.001673	Precuneus Cortex
-10	-3	12	1.056062	0.010858	Left Thalamus
-30	42	25	1.311266	0.011709	Frontal Pole
-30	15	12	2.492637	0.000628	Insular Cortex

Supplementary table 2. Regions showing a significant (time-point x group) interaction for *Granger causality analysis* seeded on the anterior insula. Coordinates are reported in MNI (Montreal Neurological Institute) space.

x	y	z	F	p	Label
36	3	9	12.812340	0.001281	Insular Cortex
30	12	-3	12.174595	0.001621	Right Putamen
27	-12	69	9.116673	0.005354	Precentral Gyrus
13	-3	42	9.909242	0.003884	Cingulate Gyrus, anterior division
-6	-39	45	9.455013	0.004663	Cingulate Gyrus, posterior division
-9	-63	57	10.289183	0.003340	Precuneus Cortex
-63	-39	36	12.237898	0.001584	Supramarginal Gyrus, anterior division

Supplementary table 3. Regions influenced by the anterior insula showing a significant difference between V7 and V1 in responders. Coordinates are reported in the MNI (Montreal Neurological Institute) space.

x	y	z	t	p	Label
60	24	21	-4.157842	0.000260	Inferior Frontal Gyrus, pars triangularis
33	12	-3	-3.346891	0.002274	Insular cortex
10	6	57	-3.259043	0.002853	Juxtapositional Lobule Cortex
3	36	18	2.706012	0.011287	Cingulate Gyrus, anterior division
-3	-9	57	-4.029006	0.000370	Juxtapositional Lobule Cortex
-9	-12	48	-3.627500	0.001088	Juxtapositional Lobule Cortex
-48	-72	-30	2.939507	0.006391	Cerebellum left Crus I

Supplementary table 4. Regions influenced by the anterior insula showing a significant difference between V7 and V1 in nonresponders. Coordinates are reported in the MNI

x	y	z	t	p	Label
51	18	42	-3.656260	0.001008	Middle Frontal Gyrus
51	-54	-21	2.810747	0.008766	Inferior Temporal Gyrus, temporococipital part
39	3	12	3.456738	0.001708	Central Opercular Cortex
27	12	3	2.947619	0.006264	Right Putamen
-12	-66	63	3.103135	0.004244	Lateral Occipital Cortex, superior division
-12	-78	3	-3.230455	0.003070	Intracalcarine Cortex
-45	15	-3	3.454878	0.001716	Frontal Operculum Cortex
-54	-30	45	3.344527	0.002288	Supramarginal Gyrus, anterior division
-64	-42	36	2.870195	0.007582	Supramarginal Gyrus, posterior division

(Montreal Neurological Institute) space.

Supplementary table 5. Comparison of *Granger Causality* maps seeded the Anterior Insula at V7 between the propranolol facilitated therapy group and the placebo-controlled group. Coordinates are reported in the MNI (Montreal Neurological Institute) space.

x	y	z	t	p	Label
42	-45	45	3.139160	0.003874	Superior Parietal Lobule
33	6	-12	3.149858	0.003771	Insular Cortex
-3	-33	51	3.167292	0.003607	Precentral Gyrus
-45	-3	35	3.104463	0.004230	Precentral Gyrus
-57	-30	42	3.715605	0.000861	Supramarginal gyrus, anterior division

IV. Discussion

1) Synthèse des principaux résultats de la thèse

Dans ce travail de thèse, nous avons confirmé par méta-analyse l'existence d'une hypoactivation du striatum ventral (faisant partie du réseau de saillance) chez les patients souffrant de schizophrénie lors de l'anticipation d'une récompense, et que cette hypoactivation était corrélée aux symptômes positifs de schizophrénie, indépendamment de la prise d'antipsychotiques. Nous avons ensuite pu valider expérimentalement une méthode de capture hallucinatoire, qui a permis de montrer de manière dynamique le rôle médiateur que pouvait jouer ce même réseau de saillance dans la survenue de symptômes intrusifs, tels que les hallucinations. Enfin, nous avons pu tester l'importance du rôle modulateur de l'insula antérieure (faisant également partie du réseau de saillance) dans la diminution des reviviscences post-traumatiques dans le TPST, permettant ainsi que formuler des hypothèses transdiagnostiques quant aux possibles mécanismes de l'intrusivité mentale dans ces deux pathologies.

2) Points communs et différences entre hallucinations et reviviscences

Les hallucinations, retrouvées chez 70 % des patients souffrants de schizophrénie (Andreasen & Flaum, 1991), sont également très présentes chez les patients souffrant de TSPT (Anketell et al., 2010; Brewin & Patel, 2010; Butler et al., 1996). Notamment, au sein des populations de vétérans de guerre, chez qui la prévalence du TSPT est importante. Les études rapportent des prévalences d'hallucinations acoustico-verbales oscillant entre 50 et 67 %. Néanmoins, sur le plan clinique, la phénoménologie des hallucinations dans le TSPT et dans la schizophrénie semble différente (McCarthy-Jones & Longden, 2015; Veerapa, 2018). En effet, les patients souffrant d'un TPST reconnaissent généralement les hallucinations comme auto-générées, alors qu'elles sont perçues comme potentiellement d'origine externe dans la schizophrénie (Anketell et al., 2010; Brewin & Patel, 2010) ou les troubles de personnalité borderline (Slotema et al., 2018). Par ailleurs, même s'il existe beaucoup de points communs entre les deux types d'hallucinations, celles présentes chez les patients souffrant d'un TPST ont un contenu fortement lié au psychotraumatisme (Anketell et al., 2010), et sont souvent attribuées à des sources ou des personnes connues (Anketell et al., 2010; Brewin & Patel, 2010).

Les reviviscences post-traumatiques semblent à ce titre différentes de ces deux types d'hallucinations d'un point de vue phénoménologique. En effet, les reviviscences se définissent dans le critère B du DSM-5 (American Psychiatric Association, 2013) comme le fait de « revivre l'évènement traumatique exactement comme il s'est produit, avec des

sensations physiologiques et/ou psychologiques identiques à celles vécues lors de l'expérience traumatique ». Ce critère n'est pas toujours retrouvé dans les hallucinations présentes chez les patients souffrant de TPST. En effet, même si certaines études retrouvent un lien significatif entre traumatisme et contenu de hallucinations (Gracie et al., 2007), beaucoup d'autres ne le retrouvent pas (Gaudiano & Zimmerman, 2010; Hamner, 1997), remettant en question la force, voire la nature possiblement causale de cette association.

Pour autant, nous avons vu que le réseau de saillance était impliqué à la fois dans les expériences hallucinatoires retrouvées dans la schizophrénie et dans les reviviscences post-traumatiques retrouvées dans le TSPT. Les bases neurobiologiques de ces deux phénomènes sont pourtant habituellement considérées comme différentes. L'une des hypothèses prédominantes pour rendre compte des symptômes positifs de la schizophrénie, et par extension des hallucinations, est l'hypothèse dopaminergique, alors que l'hypothèse noradrénergique est prépondérante dans le TSPT et les reviviscences post-traumatiques. Les neurones dopaminergiques (de la voie mésolimbique) semblent en effet impliqués dans la schizophrénie. Des études ont précocement montré que l'administration d'amphétamines, qui augmentait le niveau extracellulaire de concentration en dopamine, pouvait induire des symptômes psychotiques similaires à ceux retrouvés dans la schizophrénie (Lieberman et al., 1987). D'autres éléments viennent de l'étude des mécanismes d'action des traitements antipsychotiques. Il a ainsi été montré que leur impact clinique était lié à une forte affinité pour les récepteurs dopaminergiques, en particulier les récepteurs dopaminergiques D2 (Seeman et al., 1976; Seeman & Lee, 1975). Enfin, des études d'imagerie fonctionnelle ont pu co-localiser les régions hyperactivées lors de l'administration de traitements antipsychotiques avec les régions riches en neurones dopaminergiques. Ainsi, des études de

TEP-scan (tomographie par émission de positons) ont localisé les effets des antipsychotiques sur les boucles cortico-striato-thalamiques et sur l'hippocampe (Liddle et al., 2000). Par ailleurs, de nombreux arguments sont en faveur d'une altération des récepteurs dopaminergiques D2 dans la schizophrénie, notamment les études post-mortem (Kaalund et al., 2014) et génétiques (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Les études post-mortem ont en effet montré que les changements neuropathologiques retrouvés dans la schizophrénie incluaient à la fois une augmentation des niveaux striataux de dopamine, et une augmentation de la densité des récepteurs D2 dopaminergiques (Mackay et al., 1982; Owen et al., 1978), mais aucun changement dans la densité en transporteurs de la dopamine (Pearce et al., 1990). L'hypothèse que les récepteurs D2 sont altérés dans la schizophrénie, est également supportée par les travaux de génétique qui montrent, par exemple, une association claire entre le gène DRD2 et la schizophrénie (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Enfin, certaines études ont montré que les concentrations en dopamine sont élevées dans le plasma et le liquide cérébro-spinal chez des patients avec schizophrénie, en particulier chez des patients ne prenant pas de traitement antipsychotique (Winton-Brown et al., 2014).

D'un autre côté, dans le trouble de stress post-traumatique, plusieurs études portant sur la yohimbine (un antagoniste alpha 2 adrénergique) ont montré une réponse neurochimique et comportementale importante, concordante avec une hyperactivité noradrénergique centrale dans le TPST (Charney, 2004; Pitman et al., 2012; Zoladz & Diamond, 2013). En effet, l'axe adréno-hypothalamo-hypophysaire et le système nerveux sympathique sont centraux dans la réponse au stress. Les patients souffrant de TPST ont habituellement un cortisol bas et une augmentation des niveaux en catécholamines (Yehuda,

2002; Zoladz & Diamond, 2013). Les études épigénétiques, moléculaires et endocriniennes ont confirmé une sensibilité au feedback négatif augmentée dans le TPST, avec la mise en avant du rôle de variants génétiques des gènes impliqués dans l'axe adréno-hypothalamo-hypophysaire, incluant le gène NR3CA (codant pour le récepteur aux glucocorticoïdes) et le gène FKBP5 qui participe à la régulation des récepteurs aux hormones stéroïdes (Daskalakis et al., 2013; Zannas et al., 2015). L'hypothèse retenue ici est qu'une diminution des signaux induits par les glucocorticoïdes au moment du traumatisme induirait une activation non contrôlée du système nerveux sympathique qui augmenterait alors la consolidation de la mémoire traumatique (Yehuda, 2002). Par ailleurs, de nombreuses données suggèrent que les intrusions répétées de souvenirs traumatiques favorisent la création d'une mémoire traumatique qui associe un niveau de stress élevé, et une difficulté à éteindre le souvenir (de Quervain et al., 2009; Parsons & Ressler, 2013). Ainsi, la formation de mémoire à forte valence émotionnelle est habituellement adaptative parce que le souvenir du danger, lorsqu'il est signalé de manière appropriée, joue un rôle dans la survie. Cependant, en l'absence de signal suffisant lié aux glucocorticoïdes, le stress survient lors du rappel du souvenir, et la généralisation des signaux peut entraîner une cascade de symptômes maladaptatifs. Des nombreuses données psychopathologiques ont ainsi montré des déficits dans le conditionnement de la peur et l'extinction de la peur dans le TPST (Pitman et al., 2012), des résultats confirmés à plusieurs échelles d'observation, de l'animal à l'imagerie et en génétique humaine (Duits et al., 2015).

Néanmoins cette dichotomie entre modèles noradrénergiques dans le TPST et modèles dopaminergiques dans la schizophrénie est remise en cause. Tout d'abord, comme nous l'avons proposé dans notre étude, l'implication du réseau de saillance pose la question du

rôle que pourraient jouer les circuits dopaminergiques dans le TPST. Plusieurs études proposent d'ailleurs une efficacité des antipsychotiques anti-D2 dans le traitement des reviviscences post-traumatiques dans la schizophrénie (Albert et al., 2016; Krystal et al., 2016; Villarreal et al., 2016). Les autres systèmes monoaminergiques pourraient également être impliqués (Nikolaus et al., 2010). Ainsi, plusieurs molécules appartement à la classe des *inhibiteurs de recapture de la sérotonine* et des *inhibiteurs de la recapture de la sérotonine et de la noradrénaline* ont démontré des preuves d'efficacité sur les symptômes du TPST, et notamment sur les reviviscences post-traumatiques (Akiki & Abdallah, 2018; Lee et al., 2016). Plus récemment des études de phase 2 ont proposé dans le traitement du TPST l'utilisation du *3,4-methylenedioxymethamphetamine* (MDMA) (Bahji et al., 2020), qui est une molécule présentant notamment des actions à la fois sérotoninergiques et dopaminergiques. Dans l'étude 3 de ma thèse, une analyse préliminaire complémentaire utilisant l'atlas JuSpace (Dukart et al., 2020) suggère d'ailleurs que les régions présentant une connectivité différente entre répondeurs et non répondeurs, soient riches en récepteurs noradrénergiques, mais aussi sérotoninergiques 5-HT1A (**Figure 6**).

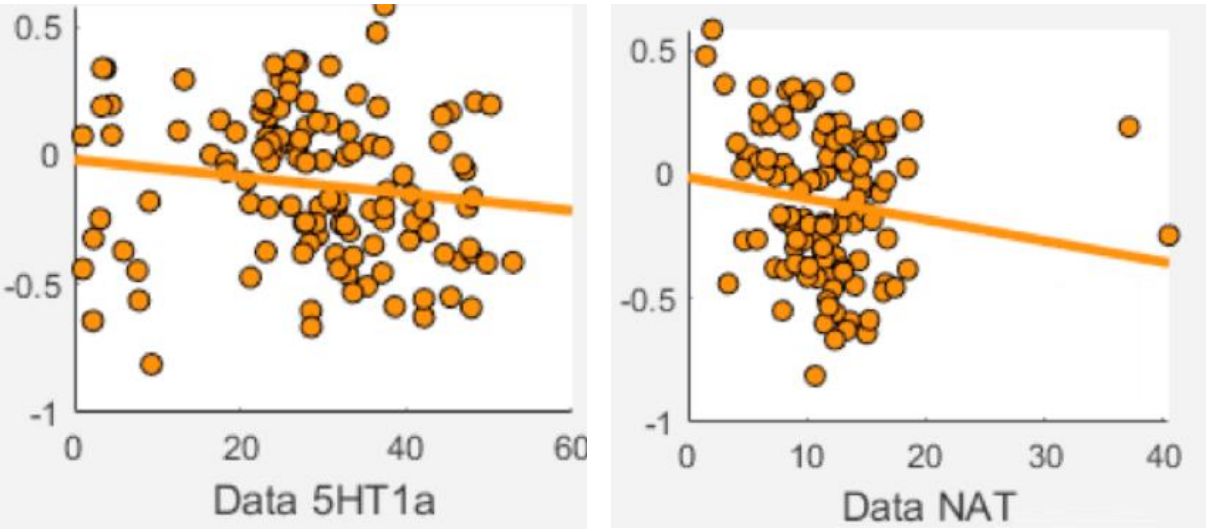


Figure 6. Corrélations entre la taille d'effet de la différence de connectivité effective en post-traitement vs pré-traitement (étude 3) et la densité en récepteurs sur les mêmes voxels (corrélation de Spearman). Les deux cartes de neurotransmetteurs montrant une corrélation significative étaient les récepteurs sérotoninergiques 5HT1a (transformation z' de Fisher = -0.2346, p = 0.012) et le transporteur de la noradrénaline NAT (transformation z' de Fisher = -0.1857, p = 0.047).

Les modèles dopaminergiques (Grace, 1991) ne sont également plus les seuls à expliquer la symptomatologie présente dans la schizophrénie, et en particulier la symptomatologie hallucinatoire. En particulier, le contenu des voix pourrait avoir une influence sur la réactivité au stress (Baumeister et al., 2019). Par ailleurs, au-delà de ces modèles, il existe depuis maintenant une dizaine d'années des arguments en faveur d'anomalies de la balance excitation/inhibition régulée par le GABA et le glutamate. Sur la base de modèles computationnels de l'architecture cérébrale, certains modes de pensée altérés dans la schizophrénie ont pu être associés à une altération des boucles inhibitrices médiées par le GABA (Jardri et al., 2016; Jardri & Denève, 2013). Au niveau macro-

anatomique, la littérature sur les réseaux intrinsèques est également instructive. En effet, les symptômes psychotiques ont été liés à un défaut d'inactivation du DMN (Whitfield-Gabrieli et al., 2009). Ce défaut d'inactivation durant une tâche est associé à une diminution de la concentration en GABA dans cette région (Hu et al., 2013). Des données cliniques et post-mortem ont également posé la question de modifications du glutamate dans la schizophrénie. L'encéphalite à auto-anticorps anti-récepteurs NMDA est une pathologie pouvant être à l'origine de syndromes psychotiques précoces. Elle est caractérisée par la présence d'anticorps anti-NMDA-R retrouvés dans le liquide cérébro-spinal (LCS) (Parenti et al., 2016). Une diminution du glutamate présent dans le LCS a également été retrouvée chez les patients souffrant de schizophrénie (Kim et al., 1980). Plusieurs études post-mortem ont enfin mis en évidence l'existence de troubles de la plasticité des récepteurs NMDA dans la schizophrénie (Humphries et al., 1996; Sokolov, 1998).

Ces observations ont été à l'origine de la théorie de l'hypofonction des récepteurs NMDA (Stone et al., 2007). Cette hypofonction des récepteurs NMDA pourrait être à l'origine d'une augmentation secondaire du glutamate qui a pu être étudiée en microdialyse chez le rat (Moghaddam et al., 1997), et qui entraîne secondairement une diminution de l'activité des interneurones GABAergiques par neurotoxicité (Olney & Farber, 1995). Cette diminution est elle-même à l'origine d'une désinhibition des neurones pyramidaux glutamatergiques (Lewis & Moghaddam, 2006) qui pourrait médier l'hyperdopaminergie mésolimbique retrouvée dans la schizophrénie (Marsman et al., 2014). Il existe, en effet, des arguments pour lier l'activité glutamatergique et l'activité dopaminergique. Plusieurs études chez le rat (David et al., 2005) et l'humain en TEP-scan (Aalto et al., 2005) montrent des modifications de la dopamine induites par antagoniste glutamatergique, le plus souvent la kétamine.

D'autres études montrent une diminution du glutamate au niveau préfrontal chez des patients ayant une schizophrénie chronique traitée, alors que ce taux est élevé dans le cortex préfrontal et le striatum chez les patients sans traitement (Fuente-Sandoval et al., 2013; Marsman et al., 2013). Enfin, une augmentation du glutamate hippocampique a été retrouvée chez des patients avec un diagnostic de schizophrénie mais encore sans traitement (Kraguljac et al., 2013). Un travail s'est spécifiquement intéressé au lien entre niveau de glutamate et symptômes positifs, en particulier les hallucinations, dans la schizophrénie. Une augmentation du glutamate frontal et temporal a été retrouvée, associée à une augmentation des scores de PANSS (Positive and Negative Syndrom Scale), échelle associée à la gravité de la maladie, à une augmentation des symptômes positifs et à une résistance au traitement médicamenteux (Demjaha et al., 2014; Hugdahl et al., 2015).

3) Au-delà du réseau de saillance

Au total, cette thèse m'a permis de mettre en évidence l'importance du réseau de saillance dans la survenue des expériences intrusives. Néanmoins, les réseaux impliqués dans ces phénomènes sont plus larges et impliquent dans les expériences hallucinatoires un réseau bilatéral impliquant, en plus de l'insula d'autres régions cérébrales comme le gyrus précentral, l'operculum frontal, les gyri temporaux moyens et supérieurs, le lobule pariétal inferieur, et les régions hippocampique/parahippocampique (Jardri et al., 2011). Dans le trouble de stress post-traumatique, le réseau de la mémoire, impliquant en particulier le complexe hippocampique et le précuneus, semble jouer un rôle central dans la survenue et la suppression des mémoires intrusives, en particulier via une régulation par les réseaux

impliqués dans le contrôle cognitif, tel que le cortex préfrontal dorsolatéral (Mary et al., 2020).

Certaines études ont étudié de manière plus générale le rôle de l'hippocampe dans la survenue de symptômes intrusifs, indépendamment de l'étiologie. En particulier, une étude récente (Schmitz et al., 2017) a montré que l'inhibition des activités de récupération mnésique par le GABA hippocampique était un élément clé dans le contrôle inhibiteur fronto-hippocampique permettant la suppression des pensées intrusives non désirées.

Les études de cette thèse ont retrouvé de manière concordante l'importance des réseaux moteurs, en particulier dans la survenue des reviviscences post-traumatiques. Néanmoins, il n'a pas été retrouvé de lien avec l'hippocampe et le para/hippocampe. Cette région est fréquemment considérée comme faisant partie du DMN (Andrews-Hanna et al., 2014). Une explication pourrait être que la connectivité de l'hippocampe a été masquée par la connectivité du DMN dans notre étude 3 notamment. En revanche, une étude récente a proposé qu'une thérapie basée sur l'exposition prolongée augmentait la connectivité fonctionnelle entre l'hippocampe, l'amygdale et le cortex préfrontal (Zhu et al., 2018), ces deux dernières régions faisant partie des aires identifiés dans ce travail. De plus, les patients présentant un TPST semblent avoir une connectivité fonctionnelle augmentée entre l'hippocampe et l'amygdale (Sripada et al., 2012). Les liens entre réseau mnésique et réseau de saillance restent donc à préciser, et nécessitent la réalisation d'études complémentaires.

4) Implications thérapeutiques. Perspectives de l'utilisation de l'imagerie pour évaluer et prédire la réponse au traitement

Cette meilleure connaissance du rôle du réseau de saillance, en particulier dans la dynamique des réseaux de repos, suggère l'importance que pourrait prendre l'imagerie cérébrale dans la compréhension des mécanismes de réponse au traitement, et à terme, leur prédiction. Ainsi, la maîtrise de la capture hallucinatoire ouvre des perspectives pour le développement de la neuromodulation neuro-naviguée (ClinicalTrials.gov : NCT01373866) et pour l'utilisation du neurofeedback permettant de détecter les hallucinations en temps réel, et à terme de développer de nouvelles thérapies non-pharmacologiques (de Pierrefeu, Fovet, et al., 2018; Fovet et al., 2016). La connaissance de la physiopathologie des expériences intrusives semble donc prometteuse pour améliorer les traitements. Néanmoins, même si de nombreux biomarqueurs d'imagerie fonctionnelle et structurale ont été proposés pour prédire l'évolution à court et long terme dans la schizophrénie (Dazzan, 2014), aucun de ces biomarqueurs n'a semblé jusqu'alors suffisamment robuste pour être utilisé en pratique clinique courante (Fond et al., 2015).

De la même façon dans le TPST, certaines études ont cherché à identifier des biomarqueurs de réponse au traitement en IRM. En IRM structurale tout d'abord, la réponse au traitement, a été associée à un plus grand volume hippocampique (Rubin et al., 2016). Sur le plan de l'imagerie fonctionnelle, le réseau attentionnel ventral a également été proposé (Etkin et al., 2019). Une autre étude a montré l'existence d'un lien entre l'amélioration des symptômes de TPST traités par une thérapie par EMDR (Eye Movement Desensitization and Reprocessing) et une connectivité augmentée entre le gyrus frontal

médial supérieur et le pôle temporal droit, et une diminution de connectivité avec le cuneus gauche et le pôle temporal gauche. De manière générale, une réponse à la psychothérapie était retrouvée associée à une diminution de l'activité de l'amygdale et de l'insula, et une augmentation de l'activité du cortex cingulaire antérieur dorsal et de l'hippocampe. Une augmentation de l'activité de l'amygdale et de l'insula en pré-traitement était par contre associée à un échec du traitement (Fonzo, Goodkind, Oathes, Zaiko, Harvey, Peng, Weiss, Thompson, Zack, Lindley, et al., 2017; Malejko et al., 2017; Sheynin et al., 2020). La réponse au traitement par psychothérapie semble également médiée par le cortex fronto-polaire (Fonzo, Goodkind, Oathes, Zaiko, Harvey, Peng, Weiss, Thompson, Zack, Mills-Finnerty, et al., 2017), alors que la réponse aux inhibiteurs de recapture de la sérotonine semble quant à elle médiée par les aires motrices et de contrôle cognitif (MacNamara et al., 2016). Enfin, la réponse au traitement par rTMS centrée sur le cortex préfrontal dorsolatéral gauche pourrait être liée à la connectivité pré-traitement du cortex cingulaire antérieur subgénual, du DMN et du SN, encore une fois parfaitement compatible avec les résultats de cette thèse.

VI. Conclusion et perspectives

Même si l'amélioration des connaissances physiopathologiques, et la caractérisation précise des points communs et de différences entre les différents symptômes intrusifs présents dans la schizophrénie et le TPST semblent prometteuses, certaines limites de cette méthodologie restent encore à dépasser. En effet, il semble aujourd'hui possible de s'orienter encore davantage vers une médecine personnalisée, c'est-à-dire une approche compréhensive et prospective pour prévenir, diagnostiquer, traiter et surveiller une maladie de manière à obtenir des décisions individualisées optimales en matière de soins de santé (Lesko, 2007). Elle peut s'appliquer pour la prescription médicamenteuse, la psychothérapie, mais aussi l'utilisation de dispositifs de soins novateurs comme la stimulation magnétique transcrânienne répétée (rTMS). C'est ainsi qu'une étude récente a montré une diminution de l'activité de l'amygdale en utilisant le neurofeedback par IRMf en temps réel dans le TSPT (Nicholson et al., 2017). De même, dans la schizophrénie, des profils d'activations spécifiques semblent à même de détecter les hallucinations en temps réel (de Pierrefeu, Fovet, et al., 2018), ouvrant ainsi le champ d'une utilisation de la thérapie guidée par neurofeedback en temps réel dans les hallucinations (https://anr.fr/Projet-ANR-16-CE37-0015).

Néanmoins, il existe des variabilités interindividuelles importantes concernant le temps nécessaire pour obtenir une réponse au traitement, la susceptibilité à développer des effets indésirables et la dose nécessaire pour obtenir une réponse thérapeutique. Par ailleurs, les différents traitements sont aujourd'hui utilisés sur le mode de l'« essai-erreur » et il apparaît

crucial de pouvoir dépasser cette approche afin de proposer le bon traitement au bon patient, et ainsi diminuer la durée symptomatique, qui reste l'un des principaux facteurs pronostiques dans de nombreuses pathologies mentales.

Deux pistes d'amélioration semblent possibles pour faciliter la validation d'outil d'imagerie pour guider les traitements : la sélection de sous-groupes de patients qui pourraient bénéficier de l'utilisation de l'imagerie cérébrale pour personnaliser le traitement, et l'inclusion de variables cliniques et biologiques dans les algorithmes de décision. Nous avons proposé récemment un questionnaire permettant de sélectionner les patients à haut risque de développer un TSPT après un accident de la route (Leroy et al., 2019), et pour lesquels la recherche de biomarqueurs d'imagerie pourrait être pertinente. En effet, il ne semble pas possible, vu la fréquence du psychotraumatisme, de faire passer une IRM à tous les patients ayant vécu un psychotraumatisme.

D'autres stratégies permettent de prendre un compte les variables cliniques et biologiques. En effet, dans le premier épisode psychotique, de nombreux biomarqueurs potentiels ont été décrits pour prédire la réponse au traitement antipsychotique, notamment au décours d'un premier traitement. Cependant, leur généralisation en pratique clinique reste difficile, car aucun ne permet à lui seul de prédire de manière fiable la réponse. Pour pallier à ce problème, de nouvelles perspectives ont vu le jour, en particulier, grâce à l'emploi d'analyses multivariées, à même d'identifier des anomalies plus fines, telles que des patterns fonctionnels ou structuraux distribués sur l'ensemble du cerveau ou au sein de quelques régions d'intérêts (Koutsouleris et al., 2009; Misaki et al., 2010). Le gain en terme statistique est tel qu'il devient envisageable de faire de l'inférence à l'échelle de

données individuelles (Pettersson-Yeo et al., 2013). Ces méthodes, dérivées de l'apprentissage machine, permettent de catégoriser un sujet sur la base d'un enregistrement IRM ou IRMf basal (ex. déterminer le risque d'évoluer vers une schizophrénie ou de répondre à un traitement donné) : on parle donc pour désigner ces techniques de "classificateurs IRM" (Lemm et al., 2011). Après un entraînement adéquat, ces classificateurs peuvent servir d'outil diagnostique, prédictif ou pronostique, et quelques résultats préliminaires sont à dénombrer dans la détection de sujets malades (de Pierrefeu, Löfstedt, et al., 2018), à risque ou dans la prédiction de la réponse au traitement. Le développement de ces méthodes devrait, à terme, permettre d'utiliser des données cliniques, biologiques, et d'imagerie pour faire de la prédiction de la réponse au traitement dans la schizophrénie et dans le TPST.

Références bibliographiques

Aalto, S., Ihalainen, J., Hirvonen, J., Kajander, J., Scheinin, H., Tanila, H., Någren, K., Vilkman, H., Gustafsson, L. L., Syvälahti, E., & Hietala, J. (2005). Cortical glutamate-dopamine interaction and ketamine-induced psychotic symptoms in man. *Psychopharmacology*, *182*(3), 375-383. https://doi.org/10.1007/s00213-005-0092-6

Ahs, F., Sollers, J. J., Furmark, T., Fredrikson, M., & Thayer, J. F. (2009). High-frequency heart rate variability and cortico-striatal activity in men and women with social phobia. *NeuroImage*, *47*(3), 815-820. https://doi.org/10.1016/j.neuroimage.2009.05.091

Akiki, T. J., & Abdallah, C. G. (2018). Are There Effective Psychopharmacologic Treatments for PTSD? *The Journal of Clinical Psychiatry*, *80*(3). https://doi.org/10.4088/JCP.18ac12473

Albert, U., Carmassi, C., Cosci, F., De Cori, D., Di Nicola, M., Ferrari, S., Poloni, N., Tarricone, I., & Fiorillo, A. (2016). Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders : A systematized review. *International Clinical Psychopharmacology*, *31*(5), 249-258. https://doi.org/10.1097/YIC.0000000000000127

Alderson-Day, B., Diederen, K., Fernyhough, C., Ford, J. M., Horga, G., Margulies, D. S., McCarthy-Jones, S., Northoff, G., Shine, J. M., Turner, J., van de Ven, V., van Lutterveld, R., Waters, F., & Jardri, R. (2016). Auditory Hallucinations and the Brain's Resting-State Networks : Findings and Methodological Observations. *Schizophrenia Bulletin*, *42*(5), 1110-1123. https://doi.org/10.1093/schbul/sbw078

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Andreasen, N. C., & Flaum, M. (1991). Schizophrenia : The characteristic symptoms. *Schizophrenia Bulletin*, *17*(1), 27-49. https://doi.org/10.1093/schbul/17.1.27

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought : Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*(1), 29-52. https://doi.org/10.1111/nyas.12360

Anketell, C., Dorahy, M. J., Shannon, M., Elder, R., Hamilton, G., Corry, M., MacSherry, A., Curran, D., & O'Rawe, B. (2010). An exploratory analysis of voice hearing in chronic PTSD : Potential associated mechanisms. *Journal of Trauma & Dissociation: The Official Journal of the International Society for the Study of Dissociation (ISSD)*, *11*(1), 93-107. https://doi.org/10.1080/15299730903143600

Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research Reviews*, *22*(3), 229-244. https://doi.org/10.1016/S0165-0173(96)00011-2

Averbeck, B. B., & Seo, M. (2008). The Statistical Neuroanatomy of Frontal Networks in the Macaque. *PLOS Computational Biology*, *4*(4), e1000050. https://doi.org/10.1371/journal.pcbi.1000050

Bahji, A., Forsyth, A., Groll, D., & Hawken, E. R. (2020). Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder : A systematic review and meta-analysis. *Progress in*

Neuro-Psychopharmacology and Biological Psychiatry, *96*, 109735. https://doi.org/10.1016/j.pnpbp.2019.109735

Ball, T. M., Knapp, S. E., Paulus, M. P., & Stein, M. B. (2017). Brain activation during fear extinction predicts exposure success. *Depression and Anxiety*, *34*(3), 257-266. https://doi.org/10.1002/da.22583

Bamiou, D.-E., Musiek, F. E., & Luxon, L. M. (2003). The insula (Island of Reil) and its role in auditory processing : Literature review. *Brain Research Reviews*, *42*(2), 143-154. https://doi.org/10.1016/S0165-0173(03)00172-3

Bangasser, D. A., Eck, S. R., & Ordoñes Sanchez, E. (2019). Sex differences in stress reactivity in arousal and attention systems. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *44*(1), 129-139. https://doi.org/10.1038/s41386-018-0137-2

Baumeister, D., Peters, E., Pruessner, J., Howes, O., & Chadwick, P. (2019). The effects of voice content on stress reactivity : A simulation paradigm of auditory verbal hallucinations. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2019.07.019

Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., & Sharp, D. J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sciences*, *109*(12), 4690-4695. https://doi.org/10.1073/pnas.1113455109

Brewin, C. R., Gregory, J. D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders : Characteristics, neural mechanisms, and treatment implications. *Psychological Review*, *117*(1), 210-232. https://doi.org/10.1037/a0018113

Brewin, C. R., & Patel, T. (2010). Auditory pseudohallucinations in United Kingdom war veterans and civilians with posttraumatic stress disorder. *The Journal of Clinical Psychiatry*, *71*(4), 419-425. https://doi.org/10.4088/JCP.09m05469blu

Bushara, Grafman, J., & Hallett, M. (2001). Neural correlates of auditory-visual stimulus onset asynchrony detection. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *21*(1), 300-304.

Bushara, Hanakawa, T., Immisch, I., Toma, K., Kansaku, K., & Hallett, M. (2003). Neural correlates of cross-modal binding. *Nature Neuroscience*, *6*(2), 190-195. https://doi.org/10.1038/nn993

Butler, R. W., Mueser, K. T., Sprock, J., & Braff, D. L. (1996). Positive symptoms of psychosis in posttraumatic stress disorder. *Biological Psychiatry*, *39*(10), 839-844. https://doi.org/10.1016/0006-3223(95)00314-2

Butti, C., & Hof, P. R. (2010). The insular cortex : A comparative perspective. *Brain Structure and Function*, *214*(5), 477-493. https://doi.org/10.1007/s00429-010-0264-y

Cameron, O. G., & Minoshima, S. (2002). Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. *Psychosomatic Medicine*, *64*(6), 851-861. https://doi.org/10.1097/01.psy.0000038939.33335.32

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability : Implications for successful adaptation to extreme stress. *The American Journal of Psychiatry*, *161*(2), 195-216. https://doi.org/10.1176/appi.ajp.161.2.195

Chase, H. W., Loriemi, P., Wensing, T., Eickhoff, S. B., & Nickl-Jockschat, T. (2018). Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia. *Human Brain Mapping*, *39*(7), 2917-2928. https://doi.org/10.1002/hbm.24049

Clos, M., Diederen, K. M. J., Meijering, A. L., Sommer, I. E., & Eickhoff, S. B. (2014). Aberrant connectivity of areas for decoding degraded speech in patients with auditory verbal hallucinations. *Brain Structure & Function*, *219*(2), 581-594. https://doi.org/10.1007/s00429-013-0519-5

Cousijn, H., Rijpkema, M., Qin, S., van Marle, H. J. F., Franke, B., Hermans, E. J., van Wingen, G., & Fernández, G. (2010). Acute stress modulates genotype effects on amygdala processing in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(21), 9867-9872. https://doi.org/10.1073/pnas.1003514107

Craig, A. D. B. (2009). How do you feel--now? The anterior insula and human awareness. *Nature Reviews. Neuroscience*, *10*(1), 59-70. https://doi.org/10.1038/nrn2555

Critchley, H. D., Eccles, J., & Garfinkel, S. N. (2013). Chapter 6—Interaction between cognition, emotion, and the autonomic nervous system. In R. M. Buijs & D. F. Swaab (Éds.), *Handbook of Clinical Neurology* (Vol. 117, p. 59-77). Elsevier. https://doi.org/10.1016/B978-0-444-53491-0.00006-7

Daskalakis, N. P., Lehrner, A., & Yehuda, R. (2013). Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. *Endocrinology and Metabolism Clinics of North America*, *42*(3), 503-513. https://doi.org/10.1016/j.ecl.2013.05.004

David, H. N., Ansseau, M., & Abraini, J. H. (2005). Dopamine-glutamate reciprocal modulation of release and motor responses in the rat caudate-putamen and nucleus accumbens of « intact » animals. *Brain Research. Brain Research Reviews*, *50*(2), 336-360. https://doi.org/10.1016/j.brainresrev.2005.09.002

Dazzan, P. (2014). Neuroimaging biomarkers to predict treatment response in schizophrenia : The end of 30 years of solitude? *Dialogues in Clinical Neuroscience*, *16*(4), 491-503.

de Pierrefeu, A., Fovet, T., Hadj-Selem, F., Löfstedt, T., Ciuciu, P., Lefebvre, S., Thomas, P., Lopes, R., Jardri, R., & Duchesnay, E. (2018). Prediction of activation patterns preceding hallucinations in patients with schizophrenia using machine learning with structured sparsity. *Human Brain Mapping*, *39*(4), 1777-1788. https://doi.org/10.1002/hbm.23953

de Pierrefeu, Löfstedt, T., Laidi, C., Hadj-Selem, F., Bourgin, J., Hajek, T., Spaniel, F., Kolenic, M., Ciuciu, P., Hamdani, N., Leboyer, M., Fovet, T., Jardri, R., Houenou, J., & Duchesnay, E. (2018). Identifying a neuroanatomical signature of schizophrenia, reproducible across sites and stages, using machine learning with structured sparsity. *Acta Psychiatrica Scandinavica*, *138*(6), 571-580. https://doi.org/10.1111/acps.12964

de Quervain, D. J.-F., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology*, *30*(3), 358-370. https://doi.org/10.1016/j.yfrne.2009.03.002

Demjaha, A., Egerton, A., Murray, R. M., Kapur, S., Howes, O. D., Stone, J. M., & McGuire, P. K. (2014). Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biological Psychiatry*, *75*(5), e11-13. https://doi.org/10.1016/j.biopsych.2013.06.011

Diederen, K. M. J., & Fletcher, P. C. (2020). Dopamine, Prediction Error and Beyond. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, 1073858420907591. https://doi.org/10.1177/1073858420907591

Dong, D., Wang, Y., Chang, X., Luo, C., & Yao, D. (2018). Dysfunction of Large-Scale Brain Networks in Schizophrenia : A Meta-analysis of Resting-State Functional Connectivity. *Schizophrenia Bulletin*, *44*(1), 168-181. https://doi.org/10.1093/schbul/sbx034

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., van den Hout, M. A., & Baas, J. M. P. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety*, *32*(4), 239-253. https://doi.org/10.1002/da.22353

Dukart, J., Holiga, S., Rullmann, M., Lanzenberger, R., Hawkins, P. C. T., Mehta, M. A., Hesse, S., Barthel, H., Sabri, O., Jech, R., & Eickhoff, S. B. (2020). JuSpace : A tool for spatial correlation analyses of magnetic resonance imaging data with nuclear imaging derived neurotransmitter maps. *BioRxiv*, 2020.04.17.046300. https://doi.org/10.1101/2020.04.17.046300

Etkin, A., Maron-Katz, A., Wu, W., Fonzo, G. A., Huemer, J., Vértes, P. E., Patenaude, B., Richiardi, J., Goodkind, M. S., Keller, C. J., Ramos-Cejudo, J., Zaiko, Y. V., Peng, K. K., Shpigel, E., Longwell, P., Toll, R. T., Thompson, A., Zack, S., Gonzalez, B., … O'Hara, R. (2019). Using fMRI connectivity to define a treatment-resistant form of post-traumatic stress disorder. *Science Translational Medicine*, *11*(486). https://doi.org/10.1126/scitranslmed.aal3236

Fond, G., d'Albis, M.-A., Jamain, S., Tamouza, R., Arango, C., Fleischhacker, W. W., Glenthøj, B., Leweke, M., Lewis, S., McGuire, P., Meyer-Lindenberg, A., Sommer, I. E., Winter-van Rossum, I., Kapur, S., Kahn, R. S., Rujescu, D., & Leboyer, M. (2015). The promise of biological markers for treatment response in first-episode psychosis : A systematic review. *Schizophrenia Bulletin*, *41*(3), 559-573. https://doi.org/10.1093/schbul/sbv002

Fonzo, G. A., Goodkind, M. S., Oathes, D. J., Zaiko, Y. V., Harvey, M., Peng, K. K., Weiss, M. E., Thompson, A. L., Zack, S. E., Lindley, S. E., Arnow, B. A., Jo, B., Gross, J. J., Rothbaum, B. O., & Etkin, A. (2017). PTSD Psychotherapy Outcome Predicted by Brain Activation During Emotional Reactivity and Regulation. *The American Journal of Psychiatry*, *174*(12), 1163-1174. https://doi.org/10.1176/appi.ajp.2017.16091072

Fonzo, G. A., Goodkind, M. S., Oathes, D. J., Zaiko, Y. V., Harvey, M., Peng, K. K., Weiss, M. E., Thompson, A. L., Zack, S. E., Mills-Finnerty, C. E., Rosenberg, B. M., Edelstein, R., Wright, R. N., Kole, C. A., Lindley, S. E., Arnow, B. A., Jo, B., Gross, J. J., Rothbaum, B. O., & Etkin, A. (2017). Selective Effects of Psychotherapy on Frontopolar Cortical Function in PTSD. *The American Journal of Psychiatry*, *174*(12), 1175-1184. https://doi.org/10.1176/appi.ajp.2017.16091073

Fortress, A. M., Hamlett, E. D., Vazey, E. M., Aston-Jones, G., Cass, W. A., Boger, H. A., & Granholm, A.-C. E. (2015). Designer receptors enhance memory in a mouse model of Down syndrome. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *35*(4), 1343-1353. https://doi.org/10.1523/JNEUROSCI.2658-14.2015

Foussias, G., & Remington, G. (2010). Negative symptoms in schizophrenia : Avolition and Occam's razor. *Schizophrenia Bulletin*, *36*(2), 359-369. https://doi.org/10.1093/schbul/sbn094

Fovet, T., Orlov, N., Dyck, M., Allen, P., Mathiak, K., & Jardri, R. (2016). Translating Neurocognitive Models of Auditory-Verbal Hallucinations into Therapy : Using Real-time fMRI-Neurofeedback to Treat Voices. *Frontiers in Psychiatry*, *7*. https://doi.org/10.3389/fpsyt.2016.00103

Fries, W. (1984). Cortical projections to the superior colliculus in the macaque monkey : A retrograde study using horseradish peroxidase. *Journal of Comparative Neurology*, *230*(1), 55-76. https://doi.org/10.1002/cne.902300106

Friston. (2002). Beyond phrenology : What can neuroimaging tell us about distributed circuitry? *Annual Review of Neuroscience*, *25*, 221-250. https://doi.org/10.1146/annurev.neuro.25.112701.142846

Friston, Frith, C. D., & Frackowiak, R. S. J. (1993). Time-dependent changes in effective connectivity measured with PET. *Human Brain Mapping*, *1*(1), 69-79. https://doi.org/10.1002/hbm.460010108

Friston, Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1993). Functional connectivity : The principal-component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *13*(1), 5-14. https://doi.org/10.1038/jcbfm.1993.4

Fuente-Sandoval, C. de la, León-Ortíz, P., Azcárraga, M., Stephano, S., Favila, R., Díaz-Galvis, L., Alvarado-Alanis, P., Ramírez-Bermúdez, J., & Graff-Guerrero, A. (2013). Glutamate levels in the associative striatum before and after 4 weeks of antipsychotic treatment in first-episode psychosis : A longitudinal proton magnetic resonance spectroscopy study. *JAMA psychiatry*. https://doi.org/10.1001/jamapsychiatry.2013.289

Fullana, M. A., Albajes-Eizagirre, A., Soriano-Mas, C., Vervliet, B., Cardoner, N., Benet, O., Radua, J., & Harrison, B. J. (2018). Fear extinction in the human brain : A meta-analysis of fMRI studies in healthy participants. *Neuroscience and Biobehavioral Reviews*, *88*, 16-25. https://doi.org/10.1016/j.neubiorev.2018.03.002

Gaudiano, B. A., & Zimmerman, M. (2010). Evaluation of evidence for the psychotic subtyping of post-traumatic stress disorder. *The British Journal of Psychiatry: The*

Journal of Mental Science, *197*(4), 326-327. https://doi.org/10.1192/bjp.bp.110.078824

Gianaros, P. J., Sheu, L. K., Matthews, K. A., Jennings, J. R., Manuck, S. B., & Hariri, A. R. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(4), 990-999. https://doi.org/10.1523/JNEUROSCI.3606-07.2008

Gogolla, N., Takesian, A. E., Feng, G., Fagiolini, M., & Hensch, T. K. (2014). Sensory integration in mouse insular cortex reflects GABA circuit maturation. *Neuron*, *83*(4), 894-905. https://doi.org/10.1016/j.neuron.2014.06.033

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., Ortega, B. N., Zaiko, Y. V., Roach, E. L., Korgaonkar, M. S., Grieve, S. M., Galatzer-Levy, I., Fox, P. T., & Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*, *72*(4), 305-315. https://doi.org/10.1001/jamapsychiatry.2014.2206

Grace, A. A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity : A hypothesis for the etiology of schizophrenia. *Neuroscience*, *41*(1), 1-24. https://doi.org/10.1016/0306-4522(91)90196-u

Gracie, A., Freeman, D., Green, S., Garety, P. A., Kuipers, E., Hardy, A., Ray, K., Dunn, G., Bebbington, P., & Fowler, D. (2007). The association between traumatic experience, paranoia and hallucinations : A test of the predictions of psychological models. *Acta Psychiatrica Scandinavica*, *116*(4), 280-289. https://doi.org/10.1111/j.1600-0447.2007.01011.x

Graziano, M. S. A., & Cooke, D. F. (2006). Parieto-frontal interactions, personal space, and defensive behavior. *Neuropsychologia*, *44*(6), 845-859. https://doi.org/10.1016/j.neuropsychologia.2005.09.009

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain : A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253-258. https://doi.org/10.1073/pnas.0135058100

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging : Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(13), 4637-4642. https://doi.org/10.1073/pnas.0308627101

Guelfi, J.-D., & Rouillon, F. (2017). *Manuel de psychiatrie* (Elsevier Masson).

Haber, S. N. (2003). The primate basal ganglia : Parallel and integrative networks. *Journal of Chemical Neuroanatomy*, *26*(4), 317-330. https://doi.org/10.1016/j.jchemneu.2003.10.003

Hamner, M. B. (1997). Psychotic features and combat-associated PTSD. *Depression and Anxiety*, *5*(1), 34-38. https://doi.org/10.1002/(sici)1520-6394(1997)5:1<34::aid-da6>3.0.co;2-5

Hermans, E. J., van Marle, H. J. F., Ossewaarde, L., Henckens, M. J. A. G., Qin, S., van Kesteren, M. T. R., Schoots, V. C., Cousijn, H., Rijpkema, M., Oostenveld, R., & Fernández, G. (2011). Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science (New York, N.Y.)*, *334*(6059), 1151-1153. https://doi.org/10.1126/science.1209603

Hor, K., & Taylor, M. (2010). Suicide and schizophrenia : A systematic review of rates and risk factors. *Journal of Psychopharmacology (Oxford, England)*, *24*(4 Suppl), 81-90. https://doi.org/10.1177/1359786810385490

Howes, Hird, E. J., Adams, R. A., Corlett, P. R., & McGuire, P. (2020). Aberrant Salience, Information Processing, and Dopaminergic Signaling in People at Clinical High Risk for Psychosis. *Biological Psychiatry*, *88*(4), 304-314. https://doi.org/10.1016/j.biopsych.2020.03.012

Howes, McCutcheon, R., & Stone, J. (2015). Glutamate and dopamine in schizophrenia : An update for the 21st century. *Journal of Psychopharmacology (Oxford, England)*, *29*(2), 97-115. https://doi.org/10.1177/0269881114563634

Hu, Y., Chen, X., Gu, H., & Yang, Y. (2013). Resting-state glutamate and GABA concentrations predict task-induced deactivation in the default mode network. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *33*(47), 18566-18573. https://doi.org/10.1523/JNEUROSCI.1973-13.2013

Hugdahl, K., Craven, A. R., Nygård, M., Løberg, E.-M., Berle, J. Ø., Johnsen, E., Kroken, R., Specht, K., Andreassen, O. A., & Ersland, L. (2015). Glutamate as a mediating transmitter for auditory hallucinations in schizophrenia : A (1)H MRS study. *Schizophrenia Research*, *161*(2-3), 252-260. https://doi.org/10.1016/j.schres.2014.11.015

Humphries, C., Mortimer, A., Hirsch, S., & de Belleroche, J. (1996). NMDA receptor mRNA correlation with antemortem cognitive impairment in schizophrenia. *Neuroreport*, *7*(12), 2051-2055. https://doi.org/10.1097/00001756-199608120-00040

Ibañez, A., Gleichgerrcht, E., & Manes, F. (2010). Clinical effects of insular damage in humans. *Brain Structure & Function*, *214*(5-6), 397-410. https://doi.org/10.1007/s00429-010-0256-y

Ide, J. S., Shenoy, P., Yu, A. J., & Li, C. R. (2013). Bayesian Prediction and Evaluation in the Anterior Cingulate Cortex. *Journal of Neuroscience*, *33*(5), 2039-2047. https://doi.org/10.1523/JNEUROSCI.2201-12.2013

Isingrini, E., Perret, L., Rainer, Q., Amilhon, B., Guma, E., Tanti, A., Martin, G., Robinson, J., Moquin, L., Marti, F., Mechawar, N., Williams, S., Gratton, A., & Giros, B. (2016). Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. *Nature Neuroscience*, *19*(4), 560-563. https://doi.org/10.1038/nn.4245

Jardri, R., & Denève, S. (2013). Circular inferences in schizophrenia. *Brain: A Journal of Neurology*, *136*(Pt 11), 3227-3241. https://doi.org/10.1093/brain/awt257

Jardri, R., Hugdahl, K., Hughes, M., Brunelin, J., Waters, F., Alderson-Day, B., Smailes, D., Sterzer, P., Corlett, P. R., Leptourgos, P., Debbané, M., Cachia, A., & Denève, S. (2016). Are Hallucinations Due to an Imbalance Between Excitatory and Inhibitory Influences on the Brain? *Schizophrenia Bulletin*, *42*(5), 1124-1134. https://doi.org/10.1093/schbul/sbw075

Jardri, R., Pouchet, A., Pins, D., & Thomas, P. (2011). Cortical activations during auditory verbal hallucinations in schizophrenia : A coordinate-based meta-analysis. *The American Journal of Psychiatry*, *168*(1), 73-81. https://doi.org/10.1176/appi.ajp.2010.09101522

Jardri, R., Thomas, P., Delmaire, C., Delion, P., & Pins, D. (2013). The neurodynamic organization of modality-dependent hallucinations. *Cerebral Cortex (New York, N.Y.: 1991)*, *23*(5), 1108-1117. https://doi.org/10.1093/cercor/bhs082

Kaalund, S. S., Newburn, E. N., Ye, T., Tao, R., Li, C., Deep-Soboslay, A., Herman, M. M., Hyde, T. M., Weinberger, D. R., Lipska, B. K., & Kleinman, J. E. (2014). Contrasting changes in DRD1 and DRD2 splice variant expression in schizophrenia and affective disorders, and associations with SNPs in postmortem brain. *Molecular Psychiatry*, *19*(12), 1258-1266. https://doi.org/10.1038/mp.2013.165

Karam, E. G., Friedman, M. J., Hill, E. D., Kessler, R. C., McLaughlin, K. A., Petukhova, M., Sampson, L., Shahly, V., Angermeyer, M. C., Bromet, E. J., de Girolamo, G., de Graaf, R., Demyttenaere, K., Ferry, F., Florescu, S. E., Haro, J. M., He, Y., Karam, A. N., Kawakami, N., … Koenen, K. C. (2014). Cumulative traumas and risk thresholds : 12-month PTSD in the World Mental Health (WMH) surveys. *Depression and Anxiety*, *31*(2), 130-142. https://doi.org/10.1002/da.22169

Kay, S. R., & Sevy, S. (1990). Pyramidical model of schizophrenia. *Schizophrenia Bulletin*, *16*(3), 537-545. https://doi.org/10.1093/schbul/16.3.537

Kim, J., Yoon, S., Lee, S., Hong, H., Ha, E., Joo, Y., Lee, E. H., & Lyoo, I. K. (2020). A double-hit of stress and low-grade inflammation on functional brain network mediates posttraumatic stress symptoms. *Nature Communications*, *11*(1), 1898. https://doi.org/10.1038/s41467-020-15655-5

Kim, Kornhuber, H. H., Schmid-Burgk, W., & Holzmüller, B. (1980). Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. *Neuroscience Letters*, *20*(3), 379-382. https://doi.org/10.1016/0304-3940(80)90178-0

Koch, S. B. J., van Zuiden, M., Nawijn, L., Frijling, J. L., Veltman, D. J., & Olff, M. (2016). ABERRANT RESTING-STATE BRAIN ACTIVITY IN POSTTRAUMATIC STRESS DISORDER : A META-ANALYSIS AND SYSTEMATIC REVIEW. *Depression and Anxiety*, *33*(7), 592-605. https://doi.org/10.1002/da.22478

Koutsouleris, N., Meisenzahl, E. M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., Schmitt, G., Zetzsche, T., Decker, P., Reiser, M., Möller, H.-J., & Gaser, C. (2009). Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Archives of General Psychiatry*, *66*(7), 700-712. https://doi.org/10.1001/archgenpsychiatry.2009.62

Kraguljac, N. V., White, D. M., Reid, M. A., & Lahti, A. C. (2013). Increased Hippocampal Glutamate and Volumetric Deficits in Unmedicated Patients With Schizophrenia. *JAMA Psychiatry*, *70*(12), 1294-1302. https://doi.org/10.1001/jamapsychiatry.2013.2437

Krystal, J. H., Pietrzak, R. H., Rosenheck, R. A., Cramer, J. A., Vessicchio, J., Jones, K. M., Huang, G. D., Vertrees, J. E., Collins, J., Krystal, A. D., & Veterans Affairs Cooperative Study #504 Group. (2016). Sleep disturbance in chronic military-related PTSD : Clinical impact and response to adjunctive risperidone in the Veterans Affairs cooperative study #504. *The Journal of Clinical Psychiatry*, *77*(4), 483-491. https://doi.org/10.4088/JCP.14m09585

Kukolja, J., Schläpfer, T. E., Keysers, C., Klingmüller, D., Maier, W., Fink, G. R., & Hurlemann, R. (2008). Modeling a negative response bias in the human amygdala by noradrenergic-glucocorticoid interactions. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(48), 12868-12876. https://doi.org/10.1523/JNEUROSCI.3592-08.2008

Larøi, F., Sommer, I. E., Blom, J. D., Fernyhough, C., Ffytche, D. H., Hugdahl, K., Johns, L. C., McCarthy-Jones, S., Preti, A., Raballo, A., Slotema, C. W., Stephane, M., & Waters, F. (2012). The characteristic features of auditory verbal hallucinations in clinical and

nonclinical groups : State-of-the-art overview and future directions. *Schizophrenia Bulletin*, *38*(4), 724-733. https://doi.org/10.1093/schbul/sbs061

Lee, D. J., Schnitzlein, C. W., Wolf, J. P., Vythilingam, M., Rasmusson, A. M., & Hoge, C. W. (2016). PSYCHOTHERAPY VERSUS PHARMACOTHERAPY FOR POSTTRAUMATIC STRESS DISORDER : SYSTEMIC REVIEW AND META-ANALYSES TO DETERMINE FIRST-LINE TREATMENTS. *Depression and Anxiety*, *33*(9), 792-806. https://doi.org/10.1002/da.22511

Lefebvre, S., Demeulemeester, M., Leroy, A., Delmaire, C., Lopes, R., Pins, D., Thomas, P., & Jardri, R. (2016). Network dynamics during the different stages of hallucinations in schizophrenia. *Human Brain Mapping*, *37*(7), 2571-2586. https://doi.org/10.1002/hbm.23197

Lemm, S., Blankertz, B., Dickhaus, T., & Müller, K.-R. (2011). Introduction to machine learning for brain imaging. *NeuroImage*, *56*(2), 387-399. https://doi.org/10.1016/j.neuroimage.2010.11.004

Leroy, A., Amad, A., D'Hondt, F., Pins, D., Jaafari, N., Thomas, P., & Jardri, R. (2020). Reward anticipation in schizophrenia : A coordinate-based meta-analysis. *Schizophrenia Research*, *218*, 2-6. https://doi.org/10.1016/j.schres.2019.12.041

Leroy, A., Cottencin, O., Labreuche, J., Mascarel, P., De Pourtales, M.-A., Molenda, S., Brelinski-Biencourt, L., Paget, V., Lemogne, C., Bougerolf, T., Gregory, T., Chantelot, C., Thery, D., Cordonnier, D., Berger, M., Demarty, A.-L., Meyer, S., Warembourg, F., Duhem, S., & Vaiva, G. (2019). *FOUR QUESTIONS TO PREDICT PTSD ONE YEAR AFTER A MOTOR VEHICLE ACCIDENT*. http://dx.doi.org/10.23668/psycharchives.2659

Lesko, L. J. (2007). Personalized medicine : Elusive dream or imminent reality? *Clinical Pharmacology and Therapeutics*, *81*(6), 807-816. https://doi.org/10.1038/sj.clpt.6100204

Lewis, & Moghaddam, B. (2006). Cognitive Dysfunction in Schizophrenia : Convergence of γ-Aminobutyric Acid and Glutamate Alterations. *Archives of Neurology*, *63*(10), 1372-1376. https://doi.org/10.1001/archneur.63.10.1372

Lewis, S. J., Arseneault, L., Caspi, A., Fisher, H. L., Matthews, T., Moffitt, T. E., Odgers, C. L., Stahl, D., Teng, J. Y., & Danese, A. (2019). The epidemiology of trauma and post-traumatic stress disorder in a representative cohort of young people in England and Wales. *The Lancet. Psychiatry*, *6*(3), 247-256. https://doi.org/10.1016/S2215-0366(19)30031-8

Liddle, P. F., Lane, C. J., & Ngan, E. T. (2000). Immediate effects of risperidone on cortico-striato-thalamic loops and the hippocampus. *The British Journal of Psychiatry: The Journal of Mental Science*, *177*, 402-407. https://doi.org/10.1192/bjp.177.5.402

Lieberman, Kane, J. M., & Alvir, J. (1987). Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology*, *91*(4), 415-433. https://doi.org/10.1007/BF00216006

Mackay, A. V., Iversen, L. L., Rossor, M., Spokes, E., Bird, E., Arregui, A., Creese, I., & Synder, S. H. (1982). Increased brain dopamine and dopamine receptors in schizophrenia. *Archives of General Psychiatry*, *39*(9), 991-997. https://doi.org/10.1001/archpsyc.1982.04290090001001

MacNamara, A., Rabinak, C. A., Kennedy, A. E., Fitzgerald, D. A., Liberzon, I., Stein, M. B., & Phan, K. L. (2016). Emotion Regulatory Brain Function and SSRI Treatment in PTSD :

Neural Correlates and Predictors of Change. *Neuropsychopharmacology*, *41*(2), 611-618. https://doi.org/10.1038/npp.2015.190

Malejko, K., Abler, B., Plener, P. L., & Straub, J. (2017). Neural Correlates of Psychotherapeutic Treatment of Post-traumatic Stress Disorder : A Systematic Literature Review. *Frontiers in Psychiatry*, *8*, 85. https://doi.org/10.3389/fpsyt.2017.00085

Manoliu, A., Riedl, V., Zherdin, A., Mühlau, M., Schwerthöffer, D., Scherr, M., Peters, H., Zimmer, C., Förstl, H., Bäuml, J., Wohlschläger, A. M., & Sorg, C. (2014). Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophrenia Bulletin*, *40*(2), 428-437. https://doi.org/10.1093/schbul/sbt037

Marsman, A., Mandl, R. C. W., Klomp, D. W. J., Bohlken, M. M., Boer, V. O., Andreychenko, A., Cahn, W., Kahn, R. S., Luijten, P. R., & Hulshoff Pol, H. E. (2014). GABA and glutamate in schizophrenia : A 7 T 1H-MRS study. *NeuroImage: Clinical*, *6*, 398-407. https://doi.org/10.1016/j.nicl.2014.10.005

Marsman, A., van den Heuvel, M. P., Klomp, D. W. J., Kahn, R. S., Luijten, P. R., & Hulshoff Pol, H. E. (2013). Glutamate in schizophrenia : A focused review and meta-analysis of ^{1}H-MRS studies. *Schizophrenia Bulletin*, *39*(1), 120-129. https://doi.org/10.1093/schbul/sbr069

Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., Vallée, T., Klein-Peschanski, C., Viader, F., de la Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2020). Resilience after trauma : The role of memory suppression. *Science (New York, N.Y.)*, *367*(6479). https://doi.org/10.1126/science.aay8477

McCarthy-Jones, S., & Longden, E. (2015). Auditory verbal hallucinations in schizophrenia and post-traumatic stress disorder : Common phenomenology, common cause, common interventions? *Frontiers in Psychology*, *6*, 1071. https://doi.org/10.3389/fpsyg.2015.01071

McCurry, K. L., Frueh, B. C., Chiu, P. H., & King-Casas, B. (2020). Opponent Effects of Hyperarousal and Re-experiencing on Affective Habituation in Posttraumatic Stress Disorder. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, *5*(2), 203-212. https://doi.org/10.1016/j.bpsc.2019.09.006

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia : A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, *30*, 67-76. https://doi.org/10.1093/epirev/mxn001

McTeague, L. M., Goodkind, M. S., & Etkin, A. (2016). Transdiagnostic impairment of cognitive control in mental illness. *Journal of Psychiatric Research*, *83*, 37-46. https://doi.org/10.1016/j.jpsychires.2016.08.001

Menon. (2011). Large-scale brain networks and psychopathology : A unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483-506. https://doi.org/10.1016/j.tics.2011.08.003

Menon. (2015). Salience Network. In A. W. Toga (Éd.), *Brain Mapping* (p. 597-611). Academic Press. https://doi.org/10.1016/B978-0-12-397025-1.00052-X

Menon, & Uddin, L. Q. (2010). Saliency, switching, attention and control : A network model of insula function. *Brain Structure & Function*, *214*(5-6), 655-667. https://doi.org/10.1007/s00429-010-0262-0

Mesulam, M.-M., & Mufson, E. J. (1982). Insula of the old world monkey. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *Journal of Comparative Neurology*, *212*(1), 1-22. https://doi.org/10.1002/cne.902120102

Misaki, M., Kim, Y., Bandettini, P. A., & Kriegeskorte, N. (2010). Comparison of multivariate classifiers and response normalizations for pattern-information fMRI. *NeuroImage*, *53*(1), 103-118. https://doi.org/10.1016/j.neuroimage.2010.05.051

Moghaddam, B., Adams, B., Verma, A., & Daly, D. (1997). Activation of glutamatergic neurotransmission by ketamine : A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *17*(8), 2921-2927.

Moran, L. V., Tagamets, M. A., Sampath, H., O'Donnell, A., Stein, E. A., Kochunov, P., & Hong, L. E. (2013). Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. *Biological Psychiatry*, *74*(6), 467-474. https://doi.org/10.1016/j.biopsych.2013.02.029

Newman, M. G., Llera, S. J., Erickson, T. M., Przeworski, A., & Castonguay, L. G. (2013). Worry and generalized anxiety disorder : A review and theoretical synthesis of evidence on nature, etiology, mechanisms, and treatment. *Annual Review of Clinical Psychology*, *9*, 275-297. https://doi.org/10.1146/annurev-clinpsy-050212-185544

Nicholson, A. A., Rabellino, D., Densmore, M., Frewen, P. A., Paret, C., Kluetsch, R., Schmahl, C., Théberge, J., Neufeld, R. W. J., McKinnon, M. C., Reiss, J., Jetly, R., & Lanius, R. A. (2017). The neurobiology of emotion regulation in posttraumatic stress disorder : Amygdala downregulation via real-time fMRI neurofeedback. *Human Brain Mapping*, *38*(1), 541-560. https://doi.org/10.1002/hbm.23402

Nieuwenhuys, R. (2012). Chapter 7 - The insular cortex : A review. In M. A. Hofman & D. Falk (Éds.), *Progress in Brain Research* (Vol. 195, p. 123-163). Elsevier. https://doi.org/10.1016/B978-0-444-53860-4.00007-6

Nikolaus, S., Antke, C., Beu, M., & Müller, H.-W. (2010). Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders—Results from in vivo imaging studies. *Reviews in the Neurosciences*, *21*(2), 119-139. https://doi.org/10.1515/revneuro.2010.21.2.119

Nothdurft, H.-C. (2000). Salience from feature contrast : Additivity across dimensions. *Vision Research*, *40*(10), 1183-1201. https://doi.org/10.1016/S0042-6989(00)00031-6

Oei, N. Y. L., Veer, I. M., Wolf, O. T., Spinhoven, P., Rombouts, S. A. R. B., & Elzinga, B. M. (2012). Stress shifts brain activation towards ventral « affective » areas during emotional distraction. *Social Cognitive and Affective Neuroscience*, *7*(4), 403-412. https://doi.org/10.1093/scan/nsr024

Olney, J. W., & Farber, N. B. (1995). Glutamate Receptor Dysfunction and Schizophrenia. *Archives of General Psychiatry*, *52*(12), 998-1007. https://doi.org/10.1001/archpsyc.1995.03950240016004

O'Neill, A., Mechelli, A., & Bhattacharyya, S. (2019). Dysconnectivity of Large-Scale Functional Networks in Early Psychosis : A Meta-analysis. *Schizophrenia Bulletin*, *45*(3), 579-590. https://doi.org/10.1093/schbul/sby094

Onur, O. A., Walter, H., Schlaepfer, T. E., Rehme, A. K., Schmidt, C., Keysers, C., Maier, W., & Hurlemann, R. (2009). Noradrenergic enhancement of amygdala responses to fear. *Social Cognitive and Affective Neuroscience*, *4*(2), 119-126. https://doi.org/10.1093/scan/nsn049

Osuch, E. A., Willis, M. W., Bluhm, R., CSTS Neuroimaging Study Group, Ursano, R. J., & Drevets, W. C. (2008). Neurophysiological responses to traumatic reminders in the acute aftermath of serious motor vehicle collisions using [15O]-H2O positron emission tomography. *Biological Psychiatry*, *64*(4), 327-335. https://doi.org/10.1016/j.biopsych.2008.03.010

Owen, F., Cross, A. J., Crow, T. J., Longden, A., Poulter, M., & Riley, G. J. (1978). Increased dopamine-receptor sensitivity in schizophrenia. *Lancet (London, England)*, *2*(8083), 223-226. https://doi.org/10.1016/s0140-6736(78)91740-3

Palaniyappan, L., Simmonite, M., White, T. P., Liddle, E. B., & Liddle, P. F. (2013). Neural primacy of the salience processing system in schizophrenia. *Neuron*, *79*(4), 814-828. https://doi.org/10.1016/j.neuron.2013.06.027

Parenti, A., Jardri, R., & Geoffroy, P. A. (2016). How Anti-NMDAR Encephalitis Sheds Light on the Mechanisms Underlying Catatonia : The Neural Excitatory/Inhibitory Imbalance Model. *Psychosomatics*, *57*(3), 336-338. https://doi.org/10.1016/j.psym.2016.01.007

Parsons, R. G., & Ressler, K. J. (2013). Implications of memory modulation for post-traumatic stress and fear disorders. *Nature Neuroscience*, *16*(2), 146-153. https://doi.org/10.1038/nn.3296

Pearce, R. K., Seeman, P., Jellinger, K., & Tourtellotte, W. W. (1990). Dopamine uptake sites and dopamine receptors in Parkinson's disease and schizophrenia. *European Neurology*, *30 Suppl 1*, 9-14. https://doi.org/10.1159/000117168

Pettersson-Yeo, W., Benetti, S., Marquand, A. F., Dell'acqua, F., Williams, S. C. R., Allen, P., Prata, D., McGuire, P., & Mechelli, A. (2013). Using genetic, cognitive and multi-modal neuroimaging data to identify ultra-high-risk and first-episode psychosis at the

individual level. *Psychological Medicine*, *43*(12), 2547-2562. https://doi.org/10.1017/S003329171300024X

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., Milad, M. R., & Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews. Neuroscience*, *13*(11), 769-787. https://doi.org/10.1038/nrn3339

Pole, N. (2007). The psychophysiology of posttraumatic stress disorder : A meta-analysis. *Psychological Bulletin*, *133*(5), 725-746. https://doi.org/10.1037/0033-2909.133.5.725

Posner, M. I., & Petersen, S. E. (1990). The Attention System of the Human Brain. *Annual Review of Neuroscience*, *13*(1), 25-42. https://doi.org/10.1146/annurev.ne.13.030190.000325

Radua, J., Schmidt, A., Borgwardt, S., Heinz, A., Schlagenhauf, F., McGuire, P., & Fusar-Poli, P. (2015). Ventral Striatal Activation During Reward Processing in Psychosis : A Neurofunctional Meta-Analysis. *JAMA Psychiatry*, *72*(12), 1243-1251. https://doi.org/10.1001/jamapsychiatry.2015.2196

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676-682. https://doi.org/10.1073/pnas.98.2.676

Rangaprakash, D., Dretsch, M. N., Venkataraman, A., Katz, J. S., Denney, T. S., & Deshpande, G. (2018). Identifying disease foci from static and dynamic effective connectivity networks : Illustration in soldiers with trauma. *Human Brain Mapping*, *39*(1), 264-287. https://doi.org/10.1002/hbm.23841

Redgrave, P., Vautrelle, N., & Reynolds, J. N. J. (2011). Functional properties of the basal ganglia's re-entrant loop architecture : Selection and reinforcement. *Neuroscience*, *198*, 138-151. https://doi.org/10.1016/j.neuroscience.2011.07.060

Rubin, M., Shvil, E., Papini, S., Chhetry, B. T., Helpman, L., Markowitz, J. C., Mann, J. J., & Neria, Y. (2016). Greater hippocampal volume is associated with PTSD treatment response. *Psychiatry Research. Neuroimaging*, *252*, 36-39. https://doi.org/10.1016/j.pscychresns.2016.05.001

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421-427. https://doi.org/10.1038/nature13595

Schlosser, D. A., Fisher, M., Gard, D., Fulford, D., Loewy, R. L., & Vinogradov, S. (2014). Motivational deficits in individuals at-risk for psychosis and across the course of schizophrenia. *Schizophrenia Research*, *158*(1-3), 52-57. https://doi.org/10.1016/j.schres.2014.06.024

Schmitz, T. W., Correia, M. M., Ferreira, C. S., Prescot, A. P., & Anderson, M. C. (2017). Hippocampal GABA enables inhibitory control over unwanted thoughts. *Nature Communications*, *8*(1), 1311. https://doi.org/10.1038/s41467-017-00956-z

Schultz. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*(1), 1-27. https://doi.org/10.1152/jn.1998.80.1.1

Schultz. (2001). Reward signaling by dopamine neurons. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *7*(4), 293-302. https://doi.org/10.1177/107385840100700406

Schultz. (2010). Dopamine signals for reward value and risk : Basic and recent data. *Behavioral and Brain Functions: BBF*, *6*, 24. https://doi.org/10.1186/1744-9081-6-24

Schultz. (2013). Updating dopamine reward signals. *Current Opinion in Neurobiology*, *23*(2), 229-238. https://doi.org/10.1016/j.conb.2012.11.012

Schultz, Preuschoff, K., Camerer, C., Hsu, M., Fiorillo, C. D., Tobler, P. N., & Bossaerts, P. (2008). Explicit neural signals reflecting reward uncertainty. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *363*(1511), 3801-3811. https://doi.org/10.1098/rstb.2008.0152

Seeman, P., & Lee, T. (1975). Antipsychotic drugs : Direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science (New York, N.Y.)*, *188*(4194), 1217-1219. https://doi.org/10.1126/science.1145194

Seeman, P., Lee, T., Chau-Wong, M., & Wong, K. (1976). Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*, *261*(5562), 717-719. https://doi.org/10.1038/261717a0

Sheynin, J., Duval, E. R., King, A. P., Angstadt, M., Phan, K. L., Simon, N. M., Rauch, S. A. M., & Liberzon, I. (2020). Associations between resting-state functional connectivity and treatment response in a randomized clinical trial for posttraumatic stress disorder. *Depression and Anxiety*. https://doi.org/10.1002/da.23075

Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*, *13*(8), 334-340. https://doi.org/10.1016/j.tics.2009.05.001

Slotema, C. W., Blom, J. D., Niemantsverdriet, M. B. A., & Sommer, I. E. C. (2018). Auditory Verbal Hallucinations in Borderline Personality Disorder and the Efficacy of Antipsychotics : A Systematic Review. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00347

Sokolov, B. P. (1998). Expression of NMDAR1, GluR1, GluR7, and KA1 glutamate receptor mRNAs is decreased in frontal cortex of « neuroleptic-free » schizophrenics : Evidence on reversible up-regulation by typical neuroleptics. *Journal of Neurochemistry*, *71*(6), 2454-2464. https://doi.org/10.1046/j.1471-4159.1998.71062454.x

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(34), 12569-12574. https://doi.org/10.1073/pnas.0800005105

Sripada, R. K., King, A. P., Garfinkel, S. N., Wang, X., Sripada, C. S., Welsh, R. C., & Liberzon, I. (2012). Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience: JPN*, *37*(4), 241-249. https://doi.org/10.1503/jpn.110069

Stone, J. M., Morrison, P. D., & Pilowsky, L. S. (2007). Glutamate and dopamine dysregulation in schizophrenia—A synthesis and selective review. *Journal of Psychopharmacology (Oxford, England)*, *21*(4), 440-452. https://doi.org/10.1177/0269881106073126

van Marle, H. J. F., Hermans, E. J., Qin, S., & Fernández, G. (2009). From specificity to sensitivity : How acute stress affects amygdala processing of biologically salient stimuli. *Biological Psychiatry*, *66*(7), 649-655. https://doi.org/10.1016/j.biopsych.2009.05.014

van Marle, H. J. F., Hermans, E. J., Qin, S., & Fernández, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *NeuroImage*, *53*(1), 348-354. https://doi.org/10.1016/j.neuroimage.2010.05.070

Veerapa, E. (2018). *Y-a-t-il trop de patients diagnostiqués psychotiques ?* Lille.

Vercammen, A., Knegtering, H., den Boer, J. A., Liemburg, E. J., & Aleman, A. (2010). Auditory hallucinations in schizophrenia are associated with reduced functional connectivity of the temporo-parietal area. *Biological Psychiatry*, *67*(10), 912-918. https://doi.org/10.1016/j.biopsych.2009.11.017

Villarreal, G., Hamner, M. B., Cañive, J. M., Robert, S., Calais, L. A., Durklaski, V., Zhai, Y., & Qualls, C. (2016). Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder : A Randomized, Placebo-Controlled Trial. *The American Journal of Psychiatry*, *173*(12), 1205-1212. https://doi.org/10.1176/appi.ajp.2016.15070967

Vogt, B. A., & Pandya, D. N. (1987). Cingulate cortex of the rhesus monkey : II. Cortical afferents. *Journal of Comparative Neurology*, *262*(2), 271-289. https://doi.org/10.1002/cne.902620208

Wager, T. D., Waugh, C. E., Lindquist, M., Noll, D. C., Fredrickson, B. L., & Taylor, S. F. (2009). Brain mediators of cardiovascular responses to social threat : Part I: Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *NeuroImage*, *47*(3), 821-835. https://doi.org/10.1016/j.neuroimage.2009.05.043

Wang, X., Zhang, W., Sun, Y., Hu, M., & Chen, A. (2016). Aberrant intra-salience network dynamic functional connectivity impairs large-scale network interactions in schizophrenia. *Neuropsychologia*, *93*(Pt A), 262-270. https://doi.org/10.1016/j.neuropsychologia.2016.11.003

Waters, F., Collerton, D., Ffytche, D. H., Jardri, R., Pins, D., Dudley, R., Blom, J. D., Mosimann, U. P., Eperjesi, F., Ford, S., & Larøi, F. (2014). Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye

disease. *Schizophrenia Bulletin*, *40 Suppl 4*, S233-245. https://doi.org/10.1093/schbul/sbu036

Watkins, E. R. (2008). Constructive and unconstructive repetitive thought. *Psychological Bulletin*, *134*(2), 163-206. https://doi.org/10.1037/0033-2909.134.2.163

Weinshenker, D. (2018). Long Road to Ruin : Noradrenergic Dysfunction in Neurodegenerative Disease. *Trends in Neurosciences*, *41*(4), 211-223. https://doi.org/10.1016/j.tins.2018.01.010

Weng, Y., Qi, R., Zhang, L., Luo, Y., Ke, J., Xu, Q., Zhong, Y., Li, J., Chen, F., Cao, Z., & Lu, G. (2019). Disturbed effective connectivity patterns in an intrinsic triple network model are associated with posttraumatic stress disorder. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *40*(2), 339-349. https://doi.org/10.1007/s10072-018-3638-1

Whitfield-Gabrieli, S., Thermenos, H. W., Milanovic, S., Tsuang, M. T., Faraone, S. V., McCarley, R. W., Shenton, M. E., Green, A. I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J. D. E., & Seidman, L. J. (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(4), 1279-1284. https://doi.org/10.1073/pnas.0809141106

Wildgust, H. J., & Beary, M. (2010). Are there modifiable risk factors which will reduce the excess mortality in schizophrenia? *Journal of Psychopharmacology (Oxford, England)*, *24*(4 Suppl), 37-50. https://doi.org/10.1177/1359786810384639

Winton-Brown, T. T., Fusar-Poli, P., Ungless, M. A., & Howes, O. D. (2014). Dopaminergic basis of salience dysregulation in psychosis. *Trends in Neurosciences*, *37*(2), 85-94. https://doi.org/10.1016/j.tins.2013.11.003

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, *5*(6), 483-494. https://doi.org/10.1038/nrn1406

Wise, R. A., & Hoffman, D. C. (1992). Localization of drug reward mechanisms by intracranial injections. *Synapse*, *10*(3), 247-263. https://doi.org/10.1002/syn.890100307

Wotruba, D., Michels, L., Buechler, R., Metzler, S., Theodoridou, A., Gerstenberg, M., Walitza, S., Kollias, S., Rössler, W., & Heekeren, K. (2014). Aberrant coupling within and across the default mode, task-positive, and salience network in subjects at risk for psychosis. *Schizophrenia Bulletin*, *40*(5), 1095-1104. https://doi.org/10.1093/schbul/sbt161

Yehuda, R. (2002). Post-traumatic stress disorder. *The New England Journal of Medicine*, *346*(2), 108-114. https://doi.org/10.1056/NEJMra012941

Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., Hobfoll, S. E., Koenen, K. C., Neylan, T. C., & Hyman, S. E. (2015). Post-traumatic stress disorder. *Nature Reviews. Disease Primers*, *1*, 15057. https://doi.org/10.1038/nrdp.2015.57

Zandvakili, A., Barredo, J., Swearingen, H. R., Aiken, E. M., Berlow, Y. A., Greenberg, B. D., Carpenter, L. L., & Philip, N. S. (2020). Mapping PTSD symptoms to brain networks : A machine learning study. *Translational Psychiatry*, *10*. https://doi.org/10.1038/s41398-020-00879-2

Zannas, A. S., Provençal, N., & Binder, E. B. (2015). Epigenetics of Posttraumatic Stress Disorder : Current Evidence, Challenges, and Future Directions. *Biological Psychiatry*, *78*(5), 327-335. https://doi.org/10.1016/j.biopsych.2015.04.003

Zerbi, V., Floriou-Servou, A., Markicevic, M., Vermeiren, Y., Sturman, O., Privitera, M., von Ziegler, L., Ferrari, K. D., Weber, B., De Deyn, P. P., Wenderoth, N., & Bohacek, J. (2019). Rapid Reconfiguration of the Functional Connectome after Chemogenetic Locus Coeruleus Activation. *Neuron*, *103*(4), 702-718.e5. https://doi.org/10.1016/j.neuron.2019.05.034

Zhu, X., Suarez-Jimenez, B., Lazarov, A., Helpman, L., Papini, S., Lowell, A., Durosky, A., Lindquist, M. A., Markowitz, J. C., Schneier, F., Wager, T. D., & Neria, Y. (2018). Exposure-based therapy changes amygdala and hippocampus resting-state functional connectivity in patients with posttraumatic stress disorder. *Depression and Anxiety*, *35*(10), 974-984. https://doi.org/10.1002/da.22816

Zoladz, P. R., & Diamond, D. M. (2013). Current status on behavioral and biological markers of PTSD : A search for clarity in a conflicting literature. *Neuroscience and Biobehavioral Reviews*, *37*(5), 860-895. https://doi.org/10.1016/j.neubiorev.2013.03.024

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Titre de la Thèse : Étude du réseau de saillance dans la survenue des expériences intrusives dans la schizophrénie et le psychotrauma

Thèse d'Université – École Doctorale Biologie Santé de Lille

Mots-clés : imagerie cérébrale, réseau de saillance, psychiatrie, schizophrénie, trouble de stress post-traumatique, intrusion

RÉSUMÉ

Les êtres humains doivent être capables d'intégrer de nombreux stimuli perceptifs mais également de filtrer en priorité les seules informations dignes d'intérêt. Ces stimuli sont priorisés en fonction de leur saillance. Le réseau cérébral de la saillance est composé de l'insula antérieure, du cortex cingulaire antérieur dorsal, de l'amygdale, du striatum ventral, et de la substance noire/aire tegmentale ventrale. Ce réseau focalise l'attention et facilite l'accès à la mémoire de travail une fois qu'un évènement saillant est détecté. Le réseau de saillance joue ainsi un rôle crucial dans la balance cognitive entre stimuli externes et processus mentaux internes. De nombreuses études ont démontré l'existence de liens entre ce réseau et le stress. De même, le réseau de saillance a été impliqué dans de nombreuses pathologies psychiatriques ou neurologiques, dont la démence fronto-temporale, les troubles de l'humeur et anxieux, la schizophrénie, les addictions ou encore la douleur. Plus spécifiquement, une implication du réseau de saillance dans les expériences intrusives a été suggérée, notamment au cours des hallucinations dans la schizophrénie, et potentiellement lors des reviviscences post-traumatiques dans le trouble de stress post-traumatique. L'objectif de ce travail de thèse était d'étudier plus précisément le rôle du réseau de saillance dans les phénomènes intrusifs dans ces deux pathologies. Une première partie est consacrée à l'étude des hallucinations dans la schizophrénie, et une seconde porte sur l'étude des reviviscences post-traumatiques dans le trouble de stress post-traumatique. Nous avons tout d'abord étudié les bases neurales de la saillance dans la schizophrénie, en réalisant une méta-analyse basée sur les coordonnées fonctionnelles (en imagerie par résonance magnétique) d'études se focalisant sur les processus de récompense. Nous avons ainsi montré que l'hypoactivation du striatum ventral retrouvée chez les patients souffrant de schizophrénie lors de ces tâches était corrélée aux symptômes positifs du trouble. Plusieurs études 'trait' et 'état' ont proposé que le réseau de saillance puisse jouer un rôle modulateur dans les expériences hallucinatoires. Dans une deuxième étude, nous avons donc validé une méthode de capture hallucinatoire à même de comparer le décours temporel des aires hyperactivées dans ces expériences, avec celui des différents réseaux fonctionnels de repos, étape indispensable pour la mesure dynamique du réseau de saillance dans ces phénomènes. Enfin, dans une troisième étude, nous avons étudié le rôle joué par le réseau de saillance, et en particulier de l'insula antérieure, dans la réponse au traitement dans le trouble de stress post-traumatique. En effet, les bases neurales de la réponse au traitement sont encore peu connues, notamment via des mesures de connectivité effective. Nous avons ainsi pu montrer l'importance du rôle modulateur de l'insula antérieure dans la diminution des reviviscences post-traumatiques. Ces résultats laissent entrevoir plusieurs applications concrètes en psychiatrie. En particulier, l'amélioration des connaissances physiopathologiques des phénomènes intrusifs, à la fois dans la schizophrénie et le trouble de stress post-traumatique, avec la perspective de développer des méthodes de capture des reviviscences post-traumatiques sur le modèle de la capture hallucinatoire, ouvre des possibilités d'avancées dans le champ de la médecine personnalisée dans ces deux pathologies.

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