UNIVERSITE LILLE
ÉCOLE DOCTORALE BIOLOGIE SANTE

MEMOIRE PRESENTE EN VUE DE L'OBTENTION DU
DIPLOME D'HABILITATION A DIRIGER DES RECHERCHES

NEUROPLASTICITE ET TROUBLES PSYCHIATRIQUES : APPROCHE MULTI-ECHELLE ET TRANSDIAGNOSTIQUE

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Table des matières

Résumé court 1

Résumé long 2

A. CV & PARCOURS 4

I. Situation actuelle 5

II. Cursus universitaire 5

III. Activités cliniques 6

IV. Activités de recherche 7

1) Bibliométrie et publications 7

2) Communications 15

3) Financement 16

4) Expertise d'articles : *reviewer* 16

5) Expertises de projet de recherche 16

V. Activités d'enseignement 17

1) Activités pédagogiques 17

2) Encadrement 17

B. TRAVAUX ANTERIEURS 19

I. Plasticité âge-dépendante 23

1) Approche génétique 24

2) Approche neuro-fonctionnelle 25

II. Plasticité symptôme dépendante 41

III. La plasticité activité-dépendante 59

C. PESPECTIVES ET PROJET SCIENTIFIQUE 74

I. Objectiver la subjectivité en psychiatrie 76

II. Approche multi-échelle des facteurs environnementaux des pathologies psychiatriques sévères 78

1) Epidémiologie des facteurs environnementaux des pathologies psychiatriques sévères 80

2) Approche multi-échelle des traitements physiques utilisés en psychiatrie 85

3) Prédiction de la réponse au traitement et catatonie : approche pharmacogénétique et d'imagerie cérébrale 87

III. L'adaptation plastique à la pathologie 89

Résumé court

La neuroplasticité (NP), définie comme la capacité du système nerveux à s'adapter aux changements environnementaux, est un phénomène intrinsèque au fonctionnement cérébral et essentiel à son homéostasie. La NP est par définition impliquée dans toutes les maladies du cerveau dont les troubles psychiatriques. Les travaux présentés ici utilisent différents troubles psychiatriques comme autant de modèles pour étudier les différentes facettes de la NP de façon translationnelle (du moléculaire au comportemental) permettant alors d'améliorer la compréhension de la régulation de la NP et de son implication dans l'étiopathogénie des troubles psychiatriques et de leurs traitements. Ce mémoire, présente dans un premier temps les travaux antérieurs publiés dans cette perspective. Ces travaux interrogent plusieurs facettes de la neuroplasticité : la neuroplasticité âge-dépendante, la neuroplasticité symptôme-dépendante et la neuroplasticité exercice-dépendante. Dans la dernière partie de ce mémoire d'HDR, mes projets de recherche pour les années à venir, sont présentés en 3 axes. Le premier s'intéresse à l'objectivation de la symptomatologie psychiatrique par des méthodes informatiques. Le deuxième axe s'intéresse à une approche multi-échelle de l'environnement dans les troubles psychiatriques (génétique, imagerie et épidémiologie). Le troisième axe s'intéresse quant à lui au concept récemment développé de l'adaptation plastique à la pathologie.

Résumé long

La neuroplasticité (NP), définie comme la capacité du système nerveux à s'adapter aux changements environnementaux, est un phénomène intrinsèque au fonctionnement cérébral et essentiel à son homéostasie. La NP est par définition impliquée dans toutes les maladies du cerveau dont les troubles psychiatriques. Les travaux présentés ici utilisent différents troubles psychiatriques comme autant de modèles pour étudier les différentes facettes de la NP de façon translationnelle (du moléculaire au comportemental) permettant alors d'améliorer la compréhension de la régulation de la NP et de son implication dans l'étiopathogénie des troubles psychiatriques et de leurs traitements.

Ce mémoire, présente dans un premier temps les travaux antérieurs publiés dans cette perspective. Ces travaux interrogent plusieurs facettes de la neuroplasticité. **La neuroplasticité âge-dépendante –** La NP opère tout au long de la vie mais est régulée différemment selon les périodes de développement. Ces modifications liées à l'âge sont non seulement quantitatives (nombre de neurones impliqués) mais également qualitatives (type de modification). La régulation neuroplastique est donc dépendante de l'âge et entraine des conséquences comportementales différentes selon l'âge de survenue d'un évènement ou d'une expérience. La dimension âge-dépendante de la NP pourrait permettre d'apporter un nouveau regard sur l'étiopathogénie des troubles psychiatriques, notamment sur les troubles associés à des antécédents traumatiques fréquents : le trouble de personnalité borderline et le trouble de stress post-traumatique (PTSD). Nous présentons ici les résultats d'une étude génétique d'association dans le trouble de personnalité borderline impliquant les polymorphismes d'un gène plusieurs fois associés au PTSD (*FKBP5*) et essentiel à la régulation de l'axe du stress. Les résultats d'une comparaison de méta-analyse d'imagerie fonctionnelle entre les 2 troubles sont aussi exposés. Ces résultats mettent en évidence des voies neuro-fonctionnelles communes entre ces 2 troubles. **La neuroplasticité symptôme-dépendante –** Cette partie étudie l'hypothèse de la dysconnectivité qui correspond à un contrôle défectueux de la NP se manifestant par une intégration fonctionnelle anormale des systèmes neuronaux spécialisés indispensables aux processus sensorimoteurs et cognitifs. Les mécanismes sous-jacents associeraient des anomalies génétiques entrainant un défaut au niveau de l'architecture cérébrale, auto-entretenu ou facilité par des mécanismes neuroplastiques. Nous avons appliqué le concept de dysconnectivité à un symptôme spécifique : l'hallucination sensorielle. Les différents travaux en imagerie multimodale (fonctionnelle, DTI, volume et forme de structures et gyrification) présentés dans ce mémoire utilisent un design spécifique permettant de mettent en évidence des différences de connectivité et d'adaptation plastique liées au symptôme (en l'occurrence les hallucinations visuelles) plutôt qu'à une maladie entière (la schizophrénie). **La neuroplasticité exercice-dépendante –** Cette section s'intéresse quant à elle à un modèle de plasticité chez des sujets sans pathologie qui pourra être utilisé, dans un second temps, à visée thérapeutique

chez des jeunes patients souffrant de troubles du spectre autistique. Dans l'étude présentée, la connectivité fonctionnelle de repos (rs-FC) a été comparée chez des jeunes adultes : 15 participants novices sains avant et après un cours de batterie (séances de 30 minutes de batterie, 3 jours par semaine pendant 8 semaines) et chez 16 participants novices appariés sur l'âge.

Dans la dernière partie de ce mémoire d'HDR, mes projets de recherche pour les années à venir, sont présentés en 3 axes. Ces axes s'articulent autour des différents aspects intéressant la neuroplasticité dans les troubles psychiatriques mais avec pour modèle pathologique les pathologies psychiatriques sévères (noté SMI pour *serious mental illness*), notamment les formes sévères des troubles de l'humeur et des troubles psychotiques, incluant le syndrome catatonique, pathologies dont je m'occupe au quotidien sur le plan clinique. Le premier axe de recherche s'intéresse à l'objectivation de la symptomatologie psychiatriquee par des méthodes informatiques en s'intéressant, dans un premier temps, à la dépression sévère. S'intéresser à cette situation clinique permettra d'évaluer et d'analyser de façon objective 1) l'activité physique (nombre de pas et fréquence cardiaque), 2) évaluation et analyse de la voix (tonalité, prosodie), 3) vitesse d'exécution, 4) émotions et motricité du visage, 5) comportement social. Au-delà de l'objectivation des signes et symptômes psychiatriques, les objectifs de ce projet correspondent naturellement à l'amélioration de la précision des diagnostics psychiatriques et à la prédiction des rechutes, fréquentes dans ces pathologies. Le deuxième axe s'intéresse à une étude multi-échelle de l'environnement (i.e. « tout ce qui est différent du gène ») dans les troubles psychiatriques (génétique, imagerie et épidémiologie). Plusieurs projets seront développés dans cet axe, tels que l'épidémiologie des facteurs environnementaux dans les SMI, l'approche multi-échelle des traitements physiques (neuromodulation) utilisés dans les SMI tels que la stimulation magnétique transcrânienne et l'électro-convulsivo-thérapie, et la pharmacogénétique couplée à l'imagerie dans la prédiction de la réponse au traitement. Finalement, le dernier axe s'intéressera au concept développé récemment de l'adaptation plastique à la pathologie, mettant en évidence la nature bidirectionnelle des modifications neuroplastiques associées à l'évolution longitudinale des troubles psychiatriques, notamment à la lumière des concepts de l'économie énergétique cérébrale.

A. CV & PARCOURS

« N'est-ce pas une chose extrêmement plaisante que de voir les philosophes les plus sérieux, si sévères qu'ils soient le reste du temps avec toute certitude, en appeler sans cesse à des sentences de poètes pour assurer force et crédibilité à leur pensée ? »

F. Nietzsche , *Le Gai Savoir,* 1882

I.Situation actuelle

FONCTIONS

Sep. 2017 – Actuel	MCU-PH de psychiatrie, Faculté de médecine de Lille, Université de Lille, CHU de Lille (service de psychiatrie adulte, Unité « Pathologies résistantes et complexes »)
Nov. 2015 – Actuel	Chercheur en neurosciences, Université de Lille, CNRS, UMR9193-PsychiC-SCALab, Lille, France
Nov. 2014 – Actuel	Chercheur en neurosciences, King's College London, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, Londres, Royaume-Uni
Sep. 2017 – Actuel	Directeur scientifique, Fédération régionale de recherche en psychiatrie et santé mentale Hauts-de-France, (www.f2rsmpsy.fr)

II.Cursus universitaire

TITRES ET DIPLOMES

Sep. 2017 – Actuel	MCU-PH de psychiatrie, Faculté de médecine de Lille, Université de Lille
Sep. 2014	Thèse d'université, Ecole Doctorale Biologie Santé, Université Lille 2. Direction : Renaud Jardri et Pierre Thomas.
Nov. 2012 – Nov. 2014	Chef de clinique des universités-assistant des hôpitaux, psychiatrie, Faculté de Médecine Henri Warembourg, Université Lille 2
Nov. 2011 – Oct. 2012	Lauréat en Médecine – option Psychiatrie – du Centre Hospitalier Régional Universitaire de Lille au titre de l'année 2011
Oct. 2011	Thèse de doctorat en Médecine, Faculté de Médecine Henri Warembourg, Université Lille 2. Direction : Renaud Jardri

CURSUS MEDICAL ET SCIENTIFIQUE

Nov. 2014 – Nov.2015	Post-Doctorat au King's College London, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience
Sept. 2011 – Sept. 2014	Doctorat en neurosciences, Ecole Doctorale Biologie Santé, Université Lille 2
Sept.2009 – Sept. 2010	Master 2 Recherche de Biologie Intégrative et Physiologie spécialité Neurosciences, sous la direction du Pr P. Gorwood, Université Pierre et Marie Curie (Paris VI)
Nov. 2006 – Nov. 2011	Internat de psychiatrie, Faculté de Médecine Henri Warembourg, Université Lille 2
Sept. 2002 – Sept. 2004	Maîtrise de Sciences Biologiques et Médicales (biologie moléculaire de la cellule (2002), biologie et pathologie moléculaire (2003), génétique humaine et comparée (2004), Faculté de Médecine Henri Warembourg, Université Lille 2

2000 – 2006 Premier et Deuxième cycles des Études Médicales, Faculté de Médecine Henri Warembourg, Université Lille 2

III.Activités cliniques

J'exerce mon activité clinique, comme PH temps plein (depuis novembre 2015) puis comme MCU-PH (depuis septembre 2017), dans le service de Psychiatrie d'Adulte du Pr. Guillaume Vaiva au CHU de Lille. Je suis responsable de l'évaluation et la prise en charge des pathologies résistantes et complexes de comorbidité à travers une activité d'hospitalisation et de consultation. Le dispositif ESPPER (Evaluation et soins des Pathologies Psychiatriques Evolutives et Résistantes), construit et articulé autour du concept de *staging*, a ainsi été mis en place et s'intéresse particulièrement aux troubles psychotiques et aux troubles de l'humeur résistants et sévères. Mon activité clinique repose sur l'intégration des neurosciences cliniques (imagerie cérébrale, biologie, pharmacologie, pharmacogénétique…), des recherches thérapeutiques (traitements neuroguidés, traitements physiques : ECT, TMS, TDCS, luminothérapie) et de l'évaluation clinique (évaluations sémiologiques et cliniques standardisées, neuropsychologie). Cette activité, utilisant des méthodes de différente échelle (clinique, génétique, imagerie et traitement par neuromodulation), s'articule particulièrement bien à mes projets de travaux de recherche sur la connectivité cérébrale et la neuroplasticité dans les situations de chronicité et de résistance.

IV.Activités de recherche

1) Bibliométrie et publications

NOMBRE DE PUBLICATIONS PAR CATEGORIE ET PAR POSITION

70 publications référencées PubMed

55 publications en premier, deuxième ou dernier rang

34 publications dans des revues de rang A ou B

Période : 2012 - 2019							
Position	**Total**	**A**	**B**	**C**	**D**	**E**	**NC**
1	13	4	5	2	0	1	1
2	18	4	4	1	3	4	2
3	6	0	1	0	2	3	0
k	9	1	3	2	2	1	0
DA	24	5	7	4	1	7	0
Total	**70**	**14**	**20**	**9**	**8**	**16**	**3**

SCORES

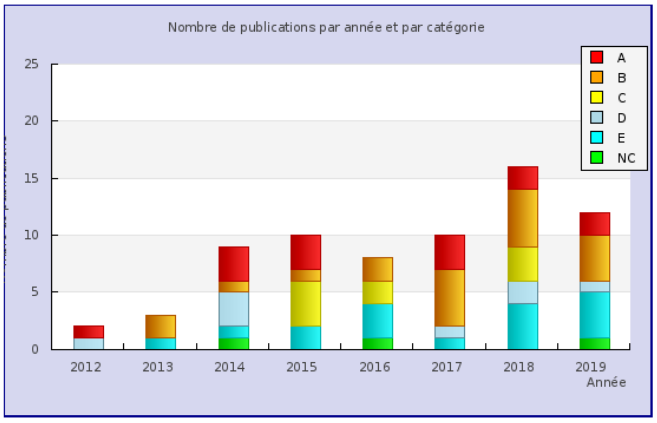
Score SIGAPS

Période : 2012 - 2019								
Année	**Total**	**A**	**B**	**C**	**D**	**E**	**NC**	**Score**
2012	2	1	0	0	1	0	0	33
2013	3	0	2	0	0	1	0	50
2014	9	3	1	0	3	1	1	138
2015	10	3	1	4	0	2	0	172
2016	8	0	2	2	0	3	1	105
2017	10	3	5	0	1	1	0	194
2018	16	2	5	3	2	4	0	188
2019	12	2	4	0	1	4	1	187
Total	**70**	**14**	**20**	**9**	**8**	**16**	**3**	**1067**

H-index = 16

Impact factor total = 282.6

Autres indicateurs



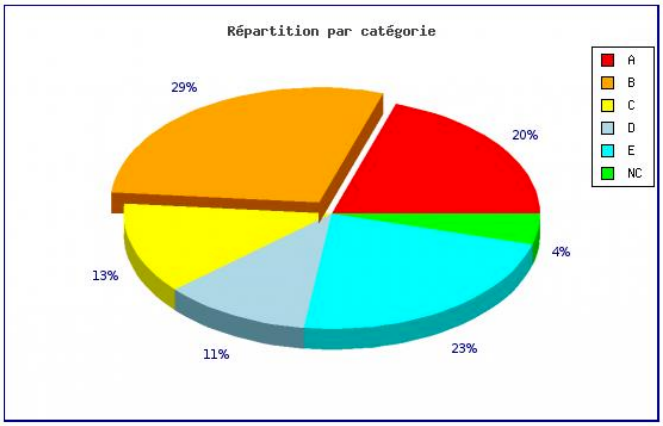


TABLEAU DES PUBLICATIONS

Auteurs	Titre	Revue	Année	IF
Majnoni d''''Intignano L, Granon O, Fovet T, Thomas P, Bonin B, Amad A	[Catatonia education in France: A cross-sectional study].	Encephale	2019	0,599
Amad A, Micoulaud-Franchi JA	[Psychiatry, psychology and the medical approach of diseases].	Rev Prat	2019	
Pignon B, Geoffroy PA, Thomas P, Roelandt JL, Amad A	Environment risk factors have different impact on bipolar and psychotic disorders: an analysis of MHGP survey.	Psychol Med	2019	5,475
Leroy A, Beigné M, Petyt G, Derambure P, Vaiva G, Amad A	Psychogenic non-epileptic seizures treated with guided transcranial direct current stimulation: A case report.	Brain Stimul	2019	6,12
Amad A, Ramoz N, Peyre H, Thomas P, Gorwood P	FKBP5 gene variants and borderline personality disorder.	J Affect Disord	2019	3,786
Eck M, Scouflaire T, Debien C, Amad A, Sannier O, Chan Chee C, Thomas P, Vaiva G, Fovet T	[Suicide in prison: Epidemiology and prevention].	Presse Med	2019	0,908
Amad A, Naudet F, Fovet T	Repetitive transcranial magnetic stimulation for depression: The non-inferiority extrapolation.	J Affect Disord	2019	3,786
Geoffroy PA, Abbassi EMBE, Maruani J, Etain B, Lejoyeux M, Amad A, Courtet P, Dubertret C, Gorwood P, Vaiva G, Bellivier F, Chevret S	Bright Light Therapy in the Morning or at Mid-Day in the Treatment of Non-Seasonal Bipolar Depressive Episodes (LuBi): Study Protocol for a Dose Research Phase I / II Trial.	Psychiatry Investig	2018	1,434
Fovet T, Horn M, Thomas P, Amad A	Is prison truly a good place to be cared for?	Acta Psychiatr Scand	2018	4,984
Leroy A, Corfiotti C, Nguyen The Tich S, Ferrafiat V, Amad A, Jardri R, Medjkane F	-Related Disorder in a 4-Year-Old Child.	Pediatrics	2018	5,515
Buyle-Bodin S, Amad A, Medjkane F, Bourion-Bedes S, Thomas P, Fovet T	[Socio-demographic and clinical characteristics of adolescents hospitalized in French units for inmates: Results of a cross-sectional study].	Encephale	2018	0,599
Kouidrat Y, Amad A	GLP-1 agonists for metabolic disorders in schizophrenia.	Schizophr. Res.	2018	3,958
Kouidrat Y, Amad A, Stubbs B, Louhou R, Renard N, Diouf M, Lalau JD, Loas G	Disordered eating behaviors as a potential obesogenic factor in schizophrenia.	Psychiatry Res	2018	2,223
Gharib A, Hieulle A, Amad A, Horn M, Hedouin V, Thomas P, Fovet T	[General medical care in French psychiatric units for inmates: A national survey].	Encephale	2018	0,599
Carton L, Dondaine T, Deheul S, Marquié C, Brigadeau F, Amad A, Devos D, Danel T,	[Supervised off-label prescribing of methylphenidate in adult ADHD].	Encephale	2018	0,599

Bordet R, Cottencin O, Gautier S, Ménard O				
Horn M, Frasca J, Amad A, Vaiva G, Thomas P, Fovet T	[Involuntary hospitalization: A survey of liberty and custody judges].	Encephale	2018	0,599
Carton L, Pignon B, Baguet A, Benradia I, Roelandt JL, Vaiva G, Thomas P, Amad A, De Timary P, Naassila M, Geoffroy PA, Rolland B	Influence of comorbid alcohol use disorders on the clinical patterns of major depressive disorder: A general population-based study.	Drug Alcohol Depend	2018	3,322
Font H, Roelandt JL, Behal H, Geoffroy PA, Pignon B, Amad A, Simioni N, Vaiva G, Thomas P, Duhamel A, Benradia I, Rolland B	Prevalence and predictors of no lifetime utilization of mental health treatment among people with mental disorders in France: findings from the 'Mental Health in General Population' (MHGP) survey.	Soc Psychiatry Psychiatr Epidemiol	2018	2,918
Pignon B, Amad A, Pelissolo A, Fovet T, Thomas P, Vaiva G, Roelandt JL, Benradia I, Rolland B, Geoffroy PA	Increased prevalence of anxiety disorders in third-generation migrants in comparison to natives and to first-generation migrants.	J Psychiatr Res	2018	4
Horn M, Pins D, Vaiva G, Thomas P, Fovet T, Amad A	[Delusional misidentification syndromes: A factor associated with violence? Literature review of case reports].	Encephale	2018	0,599
Fovet T, Geoffroy PA, Micoulaud-Franchi JA, Quiles C, Thomas P, Amad A	[Dicosemiopsy, a lexicon app of video-illustrated psychiatric semiology].	Encephale	2018	0,599
Tebeka S, Pignon B, Amad A, Le Strat Y, Brichant-Petitjean C, Thomas P, Vaiva G, Roelandt JL, Benradia I, Etain B, Rolland B, Dubertret C, Geoffroy PA	A study in the general population about sadness to disentangle the continuum from well-being to depressive disorders	J. Affect. Disord.	2018	3,786
Leroy A, Petyt G, Pignon B, Vaiva G, Jardri R, Amad A	Research Letter: Auto-activation deficit in schizophrenia: a case report	Psychol. Med.	2018	5,475
Amad A, Geoffroy PA, Micoulaud-Franchi JA, Bensamoun D, Benzerouk F, Peyre H, Yrondi A, Quiles C, Fovet T	A standardized psychiatric clinical examination for students is possible!	Ann. Med.-Psychol.	2018	0,222
Geoffroy PA, Fovet T, Yrondi A, Quiles C, Benzerouk F, Peyre H, Rolland B, Donde C, Hoertel N, Rousseau PF, Pignon B, Franchi JAM, Cancel A, Amad A	On the frontiers of psychiatric semiology!	Ann. Med.-Psychol.	2018	0,222
Pignon B, Peyre H, Szöke A, Geoffroy PA, Rolland B, Jardri R, Thomas P, Vaiva G, Roelandt JL, Benradia I, Behal H, Schürhoff F, Amad A	A latent class analysis of psychotic symptoms in the general population.	Aust N Z J Psychiatry	2017	5,084

Fovet T, Bertrand M, Horn M, Si Mohammed W, Dandelot D, Dalle MC, Thomas P, Amad A	[Involuntary psychiatric care for inmates in France: Only for "dangerous" patients?]	Encephale	2017	0,599
Pignon B, Schürhoff F, Szöke A, Geoffroy PA, Jardri R, Roelandt JL, Rolland B, Thomas P, Vaiva G, Amad A	Sociodemographic and clinical correlates of psychotic symptoms in the general population: Findings from the MHGP survey.	Schizophr. Res.	2017	3,958
Leroy A, Foucher JR, Pins D, Delmaire C, Thomas P, Roser MM, Lefebvre S, Amad A, Fovet T, Jaafari N, Jardri R	fMRI Capture of Auditory Hallucinations: Validation of the Two-Steps Method	Hum. Brain Mapp.	2017	4,927
Horn M, D'Hondt F, Gharib A, Gangloff L, Dumais A, Amad A, Thomas P, Fovet T, Pins D	Association between familiarity disorders and serious violence among inmates with schizophrenia.	Schizophr. Res.	2017	3,958
Leroy A, Naudet F, Vaiva G, Francis A, Thomas P, Amad A	Is electroconvulsive therapy an evidence-based treatment for catatonia? A systematic review and meta-analysis.	Eur Arch Psychiatry Clin Neurosci	2017	3,617
Donde C, Amad A, Nieto I, Brunoni AR, Neufeld NH, Bellivier F, Poulet E, Geoffroy PA	Transcranial direct-current stimulation (tDCS) for bipolar depression: A systematic review and meta-analysis	Prog. Neuro-Psychophar macol. Biol. Psychiatry	2017	4,185
Kouidrat Y, Amad A, Stubbs B, Moore S, Gaughran F	Surgical Management of Obesity Among People with Schizophrenia and Bipolar Disorder: a Systematic Review of Outcomes and Recommendations for Future Research	Obes. Surg.	2017	3,895
Fovet T, Micoulaud-Franchi JA, Jardri R, Linden DEJ, Amad A	Serious Games: The Future of Psychotherapy? Proposal of an Integrative Model	Psychother. Psychosom.	2017	13,122
de Labrouhe D, Plancke L, Amad A, Charrel CL, Touitou D, Bodon-Bruzel M, Thomas P, Fovet T	Hospitalization in French forensic units: Results of a patient satisfaction survey	Rev. Epidemiol. Sante Publique	2017	0,716
Rolland B, Geoffroy PA, Pignon B, Benradia I, Font H, Roelandt JL, Amad A	Alcohol Use Disorders and Immigration up to the Third Generation in France: Findings from a 39,617-Subject Survey in the General Population	Alcoholism (NY)	2017	3,183
Amad A, Radua J	Resting-state meta-analysis in Borderline Personality Disorder: Is the fronto-limbic hypothesis still valid?	J. Affect. Disord.	2017	3,786
Pignon B, Alexis Geoffroy P, Thomas P, Roelandt JL, Rolland B, Morgan C, Vaiva G, Amad A	Prevalence and clinical severity of mood disorders among first-, second- and third-generation migrants	J. Affect. Disord.	2017	3,786
Kouidrat Y, Zaitouni A, Amad A, Diouf M, Desailloud R, Loas G, Lalau JD	Skin autofluorescence (a marker for advanced glycation end products) and erectile dysfunction in diabetes	J. Diabetes Complication s	2017	2,792

Amad A, Seidman J, Draper SB, Bruchhage MMK, Lowry RG, Wheeler J, Robertson A, Williams SCR, Smith MS	Motor Learning Induces Plasticity in the Resting Brain-Drumming Up a Connection	Cereb. Cortex	2017	6,308
Quiles C, Amad A, Micoulaud-Franchi JA, Fovet T, Thomas P	Semiology of catatonic syndrome	Ann. Med.-Psychol.	2017	0,222
Haroche A, Amad A, Fovet T, Geoffroy PA, Defebvre L	Neurological diseases with psychiatric expression: Importance of neurological examination	Ann. Med.-Psychol.	2017	0,222
Geoffroy PA, Fovet T, Franchi JAM, Quiles C, Icick R, Benzerouk F, Yrondi A, Peyre H, Rolland B, Amad A	The motor semiology in psychiatry: A forgotten dimension!	Ann. Med.-Psychol.	2017	0,222
Thomas P, Amad A, Fovet T	[Schizophrenia and addictions: dangerous links].	Encephale	2016	0,742
Kouidrat Y, Amad A, Renard N, Corneille F, Lalau JD, Loas G	[Management of eating disorders in schizophrenia].	Soins Psychiatr	2016	
Geoffroy PA, Amad A	SEASONAL INFLUENCE ON MASS SHOOTINGS	Am. J. Public Health	2016	3,858
Fovet T, Micoulaud-Franchi JA, Vaiva G, Thomas P, Jardri R, Amad A	Serious game as a therapeutic tool in psychiatry: A systematic review	Enceph.-Rev. Psychiatr. Clin. Biol. Ther.	2016	0,742
Fovet T, Geoffroy PA, Vaiva G, Adins C, Thomas P, Amad A	Psychiatry in elderly prisoners	Enceph.-Rev. Psychiatr. Clin. Biol. Ther.	2016	0,742
Amad A, Ramoz N, Thomas P, Gorwood P	The age-dependent plasticity highlights the conceptual interface between borderline personality disorder and PTSD	Eur. Arch. Psych. Clin. Neurosci.	2016	3,569
Amad A, Fovet T, Geoffroy PA	Keep calm: Psychiatric disorders are organic! The power of words in medicine	Aust. N. Z. J. Psych.	2016	4,036
Caudron M, Rolland B, Deheul S, Geoffroy PA, Thomas P, Amad A	Catatonia and cannabis withdrawal: A case report	Subst. Abus.	2016	2,655
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Geoffroy PA, Fovet T, Micoulaud-Franchi JA, Boudebesse C, Thomas P, Etain B, Amad A	Bright light therapy in seasonal bipolar depressions	Enceph.-Rev. Psychiatr. Clin. Biol. Ther.	2015	0,675

Fovet T, Thomas P, Adins C, Amad A	France's forensic psychiatry provision: the long and winding road	Lancet Psychiatry	2015	5,756
Rolland B, Amad A	Off-label Treatments for Mental Health: Inappropriate or Unavoidable? A Special Issue to Help Get Through the Maze	Curr. Pharm. Design	2015	3,052
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Kouidrat Y, Amad A, Arai M, Miyashita M, Lalau JD, Loas G, Itokawa M	Advanced glycation end products and schizophrenia: A systematic review	J. Psychiatr. Res.	2015	4,465
Fovet T, Geoffroy PA, Vaiva G, Adins C, Thomas P, Amad A	Individuals With Bipolar Disorder and Their Relationship With the Criminal Justice System: A Critical Review	Psychiatr. Serv.	2015	2,335
Cachia A, Amad A, Brunelin J, Krebs MO, Plaze M, Thomas P, Jardri R	Deviations in cortex sulcation associated with visual hallucinations in schizophrenia	Mol. Psychiatr.	2015	13,314
Fovet T, Amad A, Thomas P, Jardri R	Schizophrenia and informed consent to research	Enceph.-Rev. Psychiatr. Clin. Biol. Ther.	2015	0,675
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Fovet T, Amad A	Which therapeutic applications for the serious game in psychiatry?	Eur. Psychiat.	2015	3,912
Amad A	For a free and collaborative dissemination of psychiatric education	Eur. Psychiat.	2015	3,912
Fovet T, Thomas P, Amad A	Psychiatry in prison: A specific semiology?	Ann. Med.-Psychol.	2015	0,255
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Vermersch C, Geoffroy PA, Fovet T, Thomas P, Amad A	Travel and psychotic disorders: Clinical aspects and practical recommendations	Presse Med.	2014	1,077
Amad A, Thomas P, Jardri R	The Hippocampal Complex at the Crossroad of Dimensional/Categorical Approaches	JAMA Psychiatry	2014	12,008
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Gras A, Amad A, Thomas P, Jardri R	Hallucinations and borderline personality disorder: A review	Enceph.-Rev. Psychiatr. Clin. Biol. Ther.	2014	0,698
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Amad A	New developments in the genetics of borderline personality disorder	Eur. Psychiat.	2014	3,439
Geoffroy PA, Amad A	AESP - Modern Semiotics and psychiatric diagnoses: an inseparable couple!	Eur. Psychiat.	2014	3,439
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Amad A, Geoffroy PA, Vaiva G, Thomas P	Personality and personality disorders in the elderly: Diagnostic, course and management	Enceph.-Rev. Psychiatr. Clin. Biol. Ther.	2013	0,598
Amad A, Cachia A, Thomas P, Jardri R	The Multimodal Connectivity of the Hippocampal Complex in Auditory and Visual Hallucinations	Biol. Psychiatry	2013	9,472

Kouidrat Y, Amad A, Lalau JD	Diabetes and ramadan	Corresp. M H D N	2013	0
Demeulemeester M, Amad A, Bubrovszky M, Pins D, Thomas P, Jardri R	What Is the Real Effect of 1-Hz Repetitive Transcranial Magnetic Stimulation on Hallucinations? Controlling for Publication Bias in Neuromodulation Trials	Biol. Psychiatry	2012	9,247
Geoffroy PA, Amad A, Gangloff C, Thomas P	Fibromyalgia and psychiatry: 35 years later ... What's new?	Presse Med.	2012	0,867
Kouidrat Y, Loas G, Amad A, Lalau JD, Desailloud R	Evaluation of advanced glycation endproducts (AGE) by skin autofluorescence, in a population of schizophrenic subjects.	Diabetes Metab.	2012	2,388
Amad A, Thomas P	History of mental illness in Medieval Middle East	Ann. Med.-Psychol.	2011	0,169

2) Communications

Année	Congrès	Titre de la communication
2019	Journées Tunisiennes de Radiologie, Tunis	« IRM cérébrale en psychiatrie clinique »
2019	European Congress of Radiology, Vienna	"The epidemiology of psychiatric disorders: Why brain MRI is needed?"
2018	37ème journées de la SIP	« Psychoses émergentes et migration »
2018	Congrès de l'Encéphale, Paris	« Physiopathologie du trouble borderline : vers un modèle intégratif »
2018	CFP, Nantes	« Boîte à outils translationnelle du psychiatre face aux situations complexes et résistantes »
2017	Congrès de l'Encéphale, Paris	« L'automatisme mental : de Clérambault à l'épreuve des neurosciences »
2017	Journées de la SFA	« Psychothérapies, neurobiologie et imagerie »
2017	6ème rencontre interrégionale : Pratique de l'Électro convulsivothérapie et techniques de stimulation cérébrale	« L'ECT dans le syndrome catatonique »
2017	CFP, Lyon	« L'examen clinique standardisé en psychiatrie, c'est possible ! »
2016	Congrès de l'Encéphale, Paris	« Migrants de 2ème et 3ème générations »
2016	CFP, Montpellier	« Sémiologie du syndrome catatonique »
2015	Congrès de l'Encéphale, Paris	"Des hallucinations dans un trouble de la personnalité ?"
2015	CFP, Lille	« Pour une diffusion libre et collaborative de l'enseignement psychiatrique »
2015	Institute of Psychiatry, Psychology and Neurosciences, King's College London, Neuroimaging Conference	"Neuroplasticity and psychiatric disorders : a heuristic framework"
2014	CFP, Nantes	« Actualités en génétique du trouble de personnalité borderline »
2013	CFP, Nice	« Hallucinations visuelles dans la schizophrénie : approche multimodale »
2011	Communication orale au CPNLF, Paris, 2011	« Génétique du trouble de personnalité borderline »
2010	Communication orale à la journée des étudiants au Centre de Psychiatrie et Neurosciences, Paris, décembre 2010	« Stress axis genes in borderline personality disorder"

3) Financement

2018 Financement jeune chercheur GIRCI pour le projet PHARMACOPREDICAT (40 000 euros)

2017 Prix UNESS pour le développement d'une application smartphone DICOSEMIOPSY (10 000 euros)

2014 Prix de la Fondation Thérèse et René Planiol pour l'étude du Cerveau (10 000 euros)

2013 Premier prix de la publication de l'année, Congrès Français de Psychiatrie (3 000 euros)

2012 Lauréat de la bourse Houriez (25 000 euros)

2011 Premier prix des Confrontations Psychiatriques (2 000 euros)

2011 Premier Prix de la Première Communication, CPNLF (1 500 euros)

2011 Lauréat en Médecine – option Psychiatrie – du Centre Hospitalier Régional Universitaire de Lille au titre de l'année 2011

4) Expertise d'articles : *reviewer*

Revues internationales :

- Acta Neuropsychiatrica
- Australian and New-Zealand Journal of Psychiatry
- Brain
- Comprehensive psychiatry
- European Archives of Psychiatry and Clinical Neuroscience
- European Psychiatry
- Epidemiology and Psychiatric Sciences
- Human Brain Mapping
- Journal of Affective Disorders
- Psychiatry Research
- Psychiatry Research: Neuroimaging
- Psychological Medicine
- Schizophrenia Bulletin
- Schizophrenia Research
- Scientific Report
- The British Journal of Psychiatry
- The World Journal of Biological Psychiatry

Revues nationales :

- Annales Médico-Psychologiques
- La Presse Médicale
- L'Encéphale
- Médecine/Sciences

5) Expertise de projets de recherche

PHRC, France (2015 et 2018)

V.Activités d'enseignement

1) Activités pédagogiques

COURS MAGISTRAUX

2012 – Actuel

Au moins 50 heures de cours magistraux par an :

- Etudiants en médecine de premier et deuxième cycle : psychologie médicale, enseignements dirigés de psychiatrie, neurobiologie et neurosciences, psychiatrie et thérapeutique
- Internes de DES : enseignements de psychiatrie, neurobiologie, neurosciences, psychiatrie et thérapeutique ; séminaire d'initiation à la recherche en psychiatrie et en addictologie
- Création séminaire DES de neurosciences cliniques
- Cours en DU et DIU, IFSI, master 1 et master 2

ENSEIGNEMENT PAR LA SIMULATION

2016 – Actuel Membre du club des enseignants par la simulation de la faculté de médecine de Lille et coordonnateurs de plusieurs enseignements par la simulation : module « PRENDS GARDE », « AVANT-GARDE », formation à l'ECT par la simulation, CCC par la simulation

AUTRES ACTIVITES D'ENSEIGNEMENT

- Membre fondateur et président de l'AESP (http://www.asso-aesp.fr/)
- Créateur d'une application iOS et Android de définitions illustrées des termes sémiologiques (http://dicosemiopsy.asso-aesp.fr/)
- Coordonnateur du référentiel de psychiatrie pour le deuxième cycle des études médicales (http://www.asso-aesp.fr/enseignement/1er-et-2e-cycle/referentiel-ecn/)
- Membre du groupe de coordination du eDES au niveau national
- Contenus libres en ligne : examen neurologique pour le psychiatre, examen physique pour le psychiatre, vidéos YouTube d'enseignement, examen psychiatrique standardisé, etc.
- Surveillances et corrections d'examens, examens oraux, création de dossiers cliniques

2) Encadrement

Encadrement de 2 **Master 1**

- 2016 : Marine Bohet, Master Biologie Santé, université de Lille, faculté de médecine de Lille
  « *Exploration pharmacologique et pharmacogénétique d'un cas de résistance thérapeutique à la rispéridone.* »
- 2012 : Adrien Gras, Master Biologie Santé, université de Lille, faculté de médecine de Lille
  « *Trouble de personnalité borderline, traumatismes infantiles et hallucinations : Implication de l'axe du stress* »

Encadrement de 5 **Master 2**

- 2019 : Jacques Daaboul, Master 2 Recherche de Biologie Intégrative et Physiologie spécialité Neurosciences, Université Pierre et Marie Curie (Paris VI)
  « Pharmacogénétique du lorazépam dans le syndrome catatonique »
- 2018 : Marine Bohet, Master Biologie Santé, université de Lille, faculté de médecine de Lille
  « Exploration des gènes du système dopaminergique dans le trouble de personnalité borderline et l'endophénotype impulsif »

2012-2018

- 2018 : Alaa Ali Hassan, co-encadrement Pr. Sophie Dabo, Master mathématiques et informatique appliquées aux sciences humaines et sociales, université de Lille
  « Modélisation Spatiale et cartographie du risque et de la récidive de la tentative de suicide dans la région Hauts-De-France. »
- 2018 : Alice Demesmaeker, Master méthodologie et statistiques en recherche biomédicale, Université Paris Sud
  « ALGOS-MED : Etude pharmaco-épidémiologique de l'impact des facteurs médicamenteux sur la récidive de tentatives de suicide chez les patients suicidants. »

Co-encadrement de 2 **thèses de sciences (PhD)**

- 2017-actuel : Victoire Bénard, EDBSL
  « Etude Multi-Echelles de Profils de Patients avec Risque de Suicide »
- 2015-2018: Muriel Bruchhage, co-encadrement avec Pr Steve Wiliams, Center for Neuroimaging Science, Institute of Psychiatry, King's College London
  "Investigating the cerebellar architecture in psychiatric disorders"

Autres encadrements

- Encadrement de 13 thèses de médecine
- Encadrement de 10 mémoires de DES

B. TRAVAUX ANTERIEURS

L'automne se termine
Qui pourrait comprendre
Ma mélancolie.

Yotsuya Ryu (1758)

C'est pour les loups les louves les
oufs et les youv

Booba, *Le Duc de Boulogne*, 2006

Cette partie présente de façon synthétique les travaux antérieurs réalisés et ayant été publiés. Ces travaux s'intéressent notamment aux différentes facettes de la neuroplasticité (NP) dans les troubles psychiatriques. La **NP** correspond à la **capacité du système nerveux à s'adapter, ou à se modifier, aux changements environnementaux internes et externes**. La NP, essentielle dans les processus de mémoire et d'apprentissage, est rendue possible par la formation de nouveaux neurones (neurogenèse), ainsi que par des remodelages structuraux (modification de la forme des cellules nerveuses) et fonctionnels (modification du réseau de connectivité des neurones) (Kolb et Gibb 2011). La NP joue ainsi un rôle crucial dans le développement cérébral. En effet, même si les étapes du développement cérébral (neurogenèse, migration neuronale, maturation, synaptogenèse, élagage synaptique et myélinisation) sont largement programmées sur un plan génétique, la qualité et la stabilité des connexions synaptiques sont régulées par l'expérience, et donc influencées par l'environnement. Ces processus, bien que plus intenses durant le développement, ne sont pas cantonnés à quelques périodes critiques mais existent au contraire tout au long de la vie (May 2011).

La NP peut également concerner différents niveaux de compréhension et faire référence aux systèmes moléculaires, cellulaires, neuronaux ou comportementaux. Plusieurs méthodes d'analyse peuvent alors être utilisées (imagerie cérébrale, génétique, tâches cognitives…) pour étudier la NP à différents niveaux : du moléculaire au comportemental (Figure 1) (Kolb et Gibb 2011). La NP, phénomène intrinsèque au fonctionnement cérébral et essentiel à son homéostasie, est par définition impliquée dans toutes les maladies du cerveau dont les troubles psychiatriques (Amad, Fovet, et Geoffroy 2016). L'étude de la NP a été proposée pour améliorer la compréhension de la physiopathologie des troubles psychiatriques notamment dans le but de rechercher des biomarqueurs à visée diagnostique mais aussi à visée thérapeutique (Cramer et al. 2011).

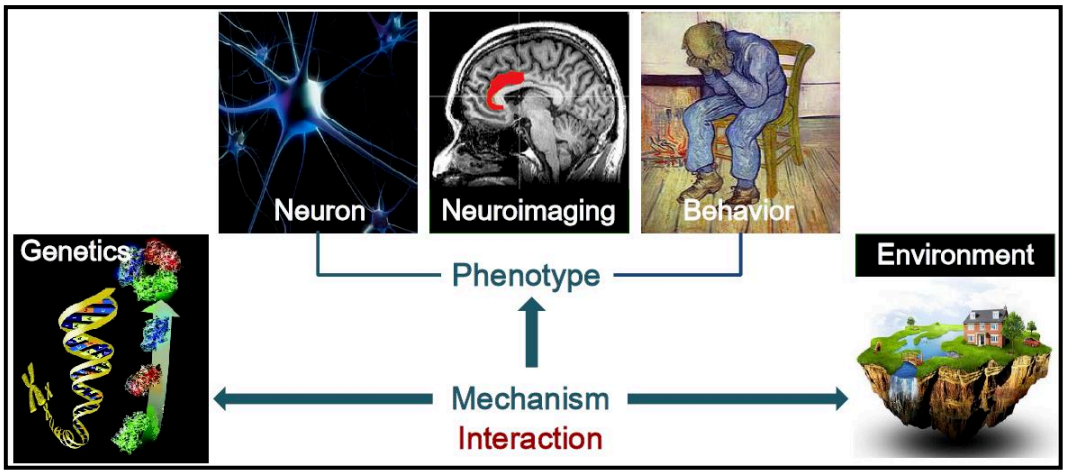

Figure 1: approche translationnelle et multimodale des troubles psychiatriques. (D'après (Ge, Schumann, et Feng 2013)).

Les troubles psychiatriques regroupent des entités très hétérogènes dont les différences sont marquées au niveau physiopathologique, étiologique, et bien entendu clinique. Ma thèse d'université défendait le point de vue que différents troubles psychiatriques pouvaient être utilisés comme autant de modèles pour étudier les différentes facettes de la NP et **l'hétérogénéité des troubles psychiatriques devient un avantage lorsqu'on les étudie sous l'angle de la NP.** Nous proposons que cette approche globale, translationnelle et "au-delà" des maladies, permettrait d'améliorer la compréhension de la régulation de la NP et de son implication dans l'étiopathogénie des troubles psychiatriques et de leurs traitements.

Dans cette première partie différentes facettes de la NP seront résumées à travers les modèles physiopathologiques distincts déjà étudiés. Une autre facette de la NP sera également présentée chez le sujet sain, la plasticité exercice-dépendante et permettra de discuter, dans les perspectives et projets de recherche, d'un essai thérapeutique d'apprentissage de la batterie chez des jeunes adultes souffrant de troubles du spectre.

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1

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Letter

Keep calm: Psychiatric disorders are organic! The power of words in medicine

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To the Editor

For a long time, psychiatric disorders were defined by the absence of an 'organic' lesion (Insel and Quirion, 2005). One vestige of this definition is the extremely frequent opposition of 'organic' or 'somatic' ('soma' means body in Greek) with 'psychiatric' disorders, not only in the international scientific literature but also in clinical practice as well as in medical teaching (for daily examples of this distinction, see Table 1). Such a dualism maintains an outdated distinction that contributes to confusion by distinguishing between 'real organic disorders', based on a failing body or 'soma', and psychiatric disorders that, by extension, would be disorders of the soul or mind.

Interestingly, in recent years, high-quality research has highlighted that the brain (an organ!), whether in its cognitive, perceptual, motivational or social functions, is involved across a range of psychiatric disorders. A highly evocative example is the work showing the neural basis of hallucinations, a classical psychiatric symptom. Functional magnetic resonance imaging (fMRI), at an individual level, shows that hallucinations of schizophrenia patients are associated with sensory cortex hyperactivation that corresponds to their symptoms (Jardri et al., 2013). Anatomically, even in the absence of no obvious macroscopic changes, structural MRI data, using machine learning methods, can differentiate psychiatric disorders (Schnack et al., 2014). Furthermore, a plethora of strong evidence has highlighted the role of susceptibility genes across a range of psychiatric disorders.

Within the perspective that such data provide, all medical disorders, including psychiatric, are organic or somatic and thus medical language must be updated, across international literature, medical teaching and clinical practice. Consequently, we propose that, when possible, the known specific etiologies should be listed, such as metabolic, cardiovascular, traumatic or infectious causes, rather than the collective term organic. If a dichotomy is to be maintained, the terms 'psychiatric disorder' and 'non-psychiatric disorder' would be preferable.

Psychiatric disorders are as organic as any other medical conditions and should be considered as such. The use of an organic/psychiatric dichotomy suggests that psychiatric disorders are not biologically 'real', with consequences that contribute to the maintenance of the stigmatization and discrimination faced by people living with psychiatric conditions. Given the power of words in medicine and the evidence of current research, the maintenance of such a dichotomy is no longer intellectually tolerable nor clinically useful for patients and their families.

Table 1. Examples of the daily use of the organic/psychiatric opposition.

International scientific literature	'*Patients were excluded if they had an organic disorder*'.
Clinical practice	From the psychiatrist: '*We will accept the patient in our unit if he doesn't present any organic disorder*'. From the non psychiatrist: '*Can you admit this patient into your unit? He doesn't present with any organic disorder*'.
Medical teaching	'*Always exclude organic causes of psychiatric symptoms*'.

Declaration of interest

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Schnack HG, Nieuwenhuis M, van Haren NEM, et al. (2014) Can structural MRI aid in clinical classification? A machine learning study in two independent samples of patients with schizophrenia, bipolar disorder and healthy subjects. *NeuroImage* 84: 299–306.

I.Plasticité âge-dépendante

La NP opère tout au long de la vie mais elle est régulée différemment selon les périodes de développement. On dit que **la neuroplasticité est âge-dépendante**. Ces variations liées à l'âge sont non seulement quantitatives (nombre de neurones et synapses impliqués) mais également qualitatives (type de modification) (Knudsen 2004). Selon le stade de développement du sujet, les conséquences d'un évènement ou d'une expérience, pourront donc avoir des conséquences différentes (Kolb et Gibb 2011).

Cette dimension de la NP peut être étudiée en s'intéressant aux conséquences d'un facteur de risque environnemental extrêmement fréquent dans les troubles psychiatriques : le traumatisme. On peut alors envisager que les conséquences d'un traumatisme pourraient être différentes selon l'âge de survenue de cet évènement. Pour illustrer cette réflexion, nous proposons de nous intéresser à des troubles psychiatriques pour lesquels des antécédents de traumatisme sont fréquemment retrouvés, voire même, font partie de la définition du trouble : le TPB et le trouble de stress post-traumatique (noté PTSD, pour *post-traumatic stress disorder*).

Le PTSD est un trouble psychiatrique secondaire à un traumatisme (accident d'avion, prise d'otage, viol, etc.) et cliniquement marqué par un syndrome de répétition (reviviscence de l'expérience traumatique), un évitement de tout ce qui rappelle l'évènement traumatique et une symptomatologie neurovégétative parfois très intense. La fréquence des antécédents traumatiques au cours du développement dans le TPB est telle qu'il a été proposé que le TPB pourrait constituer une forme complexe de PTSD (Lewis et Grenyer 2009). L'argumentation en faveur de cette hypothèse s'appuie, en plus de la fréquence des antécédents traumatiques, sur les nombreuses ressemblances entre TPB et PTSD. En effet, ces troubles présentent de très nombreux points communs: 1/ au niveau clinique, avec la dérégulation émotionnelle, le trouble du contrôle des impulsions et les difficultés interpersonnelles (van der Kolk et al. 1994), 2/ au niveau biologique, avec la dérégulation de l'axe du

stress (Wingenfeld et al. 2010), et 3/ au niveau anatomique fonctionnel, les deux troubles étant marqués par une dérégulation fronto-limbique (Shin, Rauch, et Pitman 2006).

Notre hypothèse est donc que le TPB et le PTSD pourraient être rapprochés sur le plan nosographique, et qu'une des principales différences étiologiques correspondrait à l'âge de survenue des traumatismes. Nous avons ici testé, de façon indirecte, les ressemblances potentielles entre ces troubles.

1) Approche génétique

Le TPB et le PTSD présentent ainsi de nombreux points communs et devraient, d'après notre hypothèse, présenter une vulnérabilité commune qui s'exprimerait différemment selon l'âge de survenue d'un traumatisme. Les gènes impliqués dans la régulation de l'axe hypothalamo-hypophyso-adrénergique (HPA), également appelé axe du stress, semblent être de très bons gènes candidats.

Le gène *FKBP5,* par son rôle bien connu et considéré comme essentiel dans la régulation de l'axe du stress, nous semble particulièrement intéressant pour explorer notre hypothèse. En effet, ce gène code pour la protéine FK506-binding protein 51 notée *FKBP5* (co-chaperonne de hsp 90) qui régule la sensibilité des récepteurs aux glucocorticoïdes. D'un point de vue clinique, des polymorphismes de ce gène ont, de plus, été associés à une majoration du risque de développer un trouble psychiatrique lié au stress, notamment le PTSD chez des adultes exposés à des traumatismes durant leur enfance. Par ailleurs, même si tous les mécanismes sont loin d'être élucidés, la régulation de ce gène semble différente selon les périodes de développement d'un individu (Klengel et al. 2013; Zannas et Binder 2014).

Nous présentons, ci-après, une étude dans laquelle cinq polymorphismes nucléotidiques simples (noté SNP) du gène *FKBP5* (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) ont été génotypés dans un échantillon de 101 patients caucasiens non apparentés atteints de TPB et de 111 témoins sains appariés. L'interaction entre les polymorphismes du FKBP5 et les traumatismes infantiles a également été testée. Nous avons pu mettre en évidence que tous les polymorphismes *FKBP5*

génotypés ont montré des associations significatives avec le TPB. Un effet principal de l'interaction entre rs9470080 (p = 0,01) et l'environnement du gène x (violence physique) (p = 0,01) a été trouvé. Une interaction gène x environnement (violence psychologique) a également été trouvée pour le rs3800373 (p = 0,03). Toutefois, ces interactions ne sont pas demeurées significatives après de multiples corrections de tests.

2) Approche neuro-fonctionnelle

Par ailleurs, des similitudes entre TPB et PTSD neuro-fonctionnelles ont aussi été recherchées. Nous avons ainsi effectué une méta-analyse quantitative de l'imagerie fonctionnelle à l'état de repos pour évaluer les similitudes dans l'activation cérébrale entre TPB et PTSD. Les analyses de comparaison ont révélé une diminution de l'activation dans les précuneus gauche et droit des groupes TPB et PTSD par rapport aux sujets témoins. Nous avons également mis en évidence une augmentation de l'activation dans le TPB, mais une diminution d'activation dans le PTSD, par rapport aux sujets témoins, dans les gyri cingulaires /paracingulaires antérieurs et dans le gyrus frontal supérieur gauche (Figure 2). Des comparaisons complémentaires sur un sous-groupe d'études ayant une distribution similaire selon le sexe et l'âge ont partiellement confirmé les principaux résultats, car le même schéma d'activation fonctionnelle dans le cingulum antérieur et dans le gyrus frontal supérieur gauche a été observé. Nos résultats concordent donc avec l'hypothèse selon laquelle le TPB et le PTSD partagent des voies neuro-fonctionnelles communes. Ce travail est actuellement en cours de révision dans la revue *Neuroscience and Biobehavioral Review*.

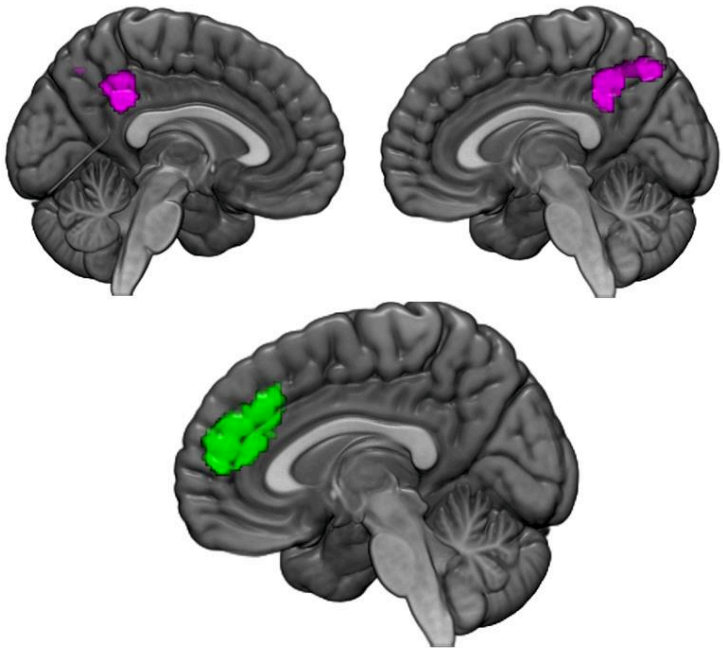

Figure 2 : clusters montrant une diminution significative de l'activation similaire entre les groupes TPB et PTSD (violet) par rapport aux sujets témoins dans les précuneus gauche et droit. D'autres régions (en vert) ont également été identifiées où le TPB a montré une augmentation significative de l'activation mais une diminution de l'activation dans le PTSD par rapport aux sujets témoins dans les gyri cingulaires /paracingulaires antérieurs et dans le gyrus frontal supérieur gauche.

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LETTER TO THE EDITOR

The age-dependent plasticity highlights the conceptual interface between borderline personality disorder and PTSD

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Letter to the Editors

Martín-Blanco et al. [1] recently wrote a stimulating paper that explored the influence of genetic variants in the hypothalamus–pituitary–adrenal (HPA) axis on the risk of borderline personality disorder (BPD) and the modulator effect of traumatic experiences in childhood. In this study, associations between *FKBP5* variants and BPD diagnosis were observed and were more significant when the presence of childhood traumas was considered.

We believe that these results can help to highlight the controversy surrounding the nature of the relationship between BPD and posttraumatic stress disorder (PTSD). Indeed, the study of Martín-Blanco et al. [1] showed that BPD has a genetic vulnerability shared with PTSD, as genetic polymorphisms in *FKBP5*—an important functional regulator of the glucocorticoid receptor complex—have also been associated with adult PTSD (for review, see [2]). Moreover, the prevalence of childhood trauma is so frequently associated with BPD [either neglect (92 %), sexual abuse (40–70 %) or physical abuse (25–73 %) [3]] that it has often been described as being conceptually and phenomenologically similar to PTSD [4, 5]. In particular, these two disorders present numerous striking similarities at the etiological, clinical, neurofunctional and neurobiological levels. These similarities are summarized in Table 1.

We propose that the conceptual interface between BPD and PTSD could be highlighted by the 'age-dependent neuroplasticity' framework, which postulates that a same experience can differentially affect the brain plasticity depending on the age of the experience [6]. Indeed, neuroplasticity, defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli, underlies not only normal development and maturation but can also occur in response to the environment or in response to disease. Even if neuroplasticity was initially thought to be limited to critical periods in development, it is now largely accepted to occur throughout the life span. There are several examples of the effect of age-dependent neuroplasticity in different diseases such as the plastic changes following cerebral injury, which vary according to the age of the patients [6]. There is also some evidence of age-dependent neuroplasticity following trauma, as it has been showed that the effects of stressors occurring early in development are stronger and more persistent in comparison with stressors occurring during adulthood [7]. Interestingly, FKBP5 is thought to be differently regulated according to the different periods of neurodevelopment [2] and is also involved in the connectivity of brain regions and circuits related to mood regulation and cognitive function [8]. Finally, the conceptual framework of 'age-dependent neuroplasticity' fits well with the dysconnectivity model of mental illness, which suggests that psychiatric symptoms are associated with impairments in brain connectivity, particularly in networks that underpin the functions of everyday human experience (i.e., the cognitive, affective, motor, motivational and social networks)

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Table 1 Similarities between borderline personality disorder (BPD) and posttraumatic stress disorder (PTSD)

Levels of comparison	Shared features between BPD and PTSD
Etiological level	High frequency of trauma Evidences for gene–environment interaction [2, 10]
Clinical level	Major disturbances in [4, 5] Emotional regulation Impulse control Reality testing Interpersonal relationships Sense of identity
Neurofunctional level	Abnormalities in frontolimbic networks [12, 13] Limbic hyperactivity and diminished recruitment of frontal brain regions
Neurobiological level	Hypothalamus–pituitary–adrenal (HPA) axis dysregulation [14, 15]
Genetic level	Association with *FKBP5* [1, 2]

[9]. Brain dysconnectivity is associated with an impaired control of synaptic plasticity, which involves both genetic and environmental factors, and leads to alterations in brain wiring, as well as impaired experience-dependent synaptic plasticity. Thus, we propose that BPD and PTSD are two sides of the same coin and that the main key difference between these disorders is the age at which traumas occur, which can differentially affect the brain connectivity and thus the psychiatric symptoms. For instance, trauma during childhood would favor the development of BPD [10], while trauma in adulthood would increase the risk of PTSD.

One of the most frequently observed criticisms when considering BPD as a kind of complex PTSD is that the existence of a risk factor (i.e., trauma) is not necessary or sufficient to explain the development of the disorder [5]. However, it is now well established that gene–environment interactions play a role in the development of both BPD [10] and PTSD [11]. Another important criticism may well be that not all individuals with BPD have a history of childhood trauma. However, clinical profiles of BPD patients appear to differ according to the severity of childhood trauma [3]. BPD with and without a history of childhood abuse could then be considered as different psychiatric disorders, and thus, a direct comparison of their clinical profiles would be of great interest. Ideally, these analyses would be performed in large well-characterized epidemiological cohorts powerful enough to detect BPD patients without a history of trauma.

Lastly, coupling methods such as imaging genetics, centered on connectivity analyses, may also improve the comprehension of the pathophysiology of BPD and PTSD. This strategy is indeed particularly adequate for the transdiagnostic approach of psychiatric disorders [9] and has proven to be powerful for identifying the mechanisms linking genes to behaviors and psychiatric disorders.

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Compliance with ethical standards

Conflict of interest No conflict of interest to disclose.

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Short communication

FKBP5 gene variants and borderline personality disorder

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ABSTRACT

Background: Genes associated with the physiological response to stress in the hypothalamic-pituitary-adrenal axis are considered as good candidates for genetic research in borderline personality disorder (BPD).
Methods: In this study, five *FKBP5* (a co-chaperone of the glucocorticoid receptor) SNPs (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) were genotyped in a sample of 101 unrelated Caucasian patients with BPD and 111 ethnically matched healthy controls. The interaction between *FKBP5* polymorphisms and childhood trauma was also tested.
Results: All *FKBP5* polymorphisms genotyped showed significant associations with BPD. A main effect of rs9470080 ($p = 0.01$) and gene x environment (physical abuse) interaction ($p = 0.01$) was found. A gene x environment (emotional abuse) interaction was also found for rs3800373 ($p = 0.03$). However, these interactions did not remain significant after multiple testing corrections.
Limitations: In this study, only 5 genetic variants were tested and thus tagging of the *FKBP5* gene was incomplete. Moreover, the sample size is moderate.
Conclusion: BPD is associated with *FKBP5* polymorphisms and several types of childhood abuse may modulate the effect between *FKBP5* SNPs and this disorder.

1. Introduction

Borderline personality disorder (BPD) is characterized by a pervasive pattern of emotional lability, disturbed cognition (such as derealization, depersonalization or hallucinations), identity disturbances, impulsivity and interpersonal difficulties (Lieb et al., 2004b). BPD is the most common personality disorder in clinical settings and is estimated to occur in 0.5–5.9% of the general population (Skodol et al., 2002).

The knowledge on the biological factors involved in the pathophysiology of BPD is still scarce. Interestingly, a genetic vulnerability has been identified with a heritability estimated between 40 and 60% (Amad et al., 2014). However, the number of association studies using the candidate gene method is low considering both the heritability and the high frequency of BPD. For now, most candidate genes studied were genes involved in the monoaminergic neurotransmitter systems (Leichsenring et al., 2011; Lieb et al., 2004b).

It has recently been proposed that genes associated with the physiological response to stress in the hypothalamic-pituitary-adrenal (HPA) axis could be good candidates for genetic research in BPD (Amad et al., 2014). In fact, many arguments support HPA axis dysregulation in BPD (Zimmerman and Choi-Kain, 2009) such as an increased diurnal salivary cortisol in women with BPD (Lieb et al., 2004a) or a non-suppression to the Dexamethasone Suppression Test (Wingenfeld et al., 2010). Moreover, epigenetic modifications have been identified in glucocorticoid receptor genes in patients with BPD (Perroud et al., 2011).

Recently, Martin-Blanco et al. have tested the association of genetic variants in the HPA axis by analyzing 47 polymorphisms in 10 HPA axis genes in BPD and controls. They found that two *FKBP5* polymorphisms (rs4713902 and rs9470079) showed significant associations with BPD (Martín-Blanco et al., 2015). Moreover, as the presence of a gene-environment interaction (G × E) is highly likely (Amad et al., 2014), these authors also explored the effect of childhood trauma in the development of BPD. They found that both *FKBP5* polymorphisms were more frequent in patients who reported childhood physical abuse and emotional neglect (Martín-Blanco et al., 2015). Interestingly, FKBP5 encodes the FK506-binding protein 5, which is involved in the regulation of glucocorticoid receptors and appears as an interesting candidate gene as it has been associated to HPA axis dysregulation in the general population and in patients with psychiatric stress-related disorders,

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Table 1
Single marker frequencies and association with borderline personality disorder.

SNP	Assoc allele	Case, control ratio counts	Case, control frequencies	Chi square	P value
rs3800373	C	143:43, 136:68	0.769, 0.667	4.986	0.0256
rs9296158	C	145:45, 131:73	0.763, 0.642	6.865	0.0088
rs737054	C	67:123, 53:153	0.353, 0.257	4.255	0.0391
rs1360780	A	140:48, 131:77	0.745, 0.630	6.032	0.014
rs9470080	A	142:50, 128:78	0.740, 0.621	6.366	0.0116

especially in adults with a history of childhood maltreatment (Zannas and Binder, 2014).

The purpose of the present study was to investigate the contribution of different polymorphisms of *FKBP5* and to explore the modulating effect of childhood abuse in an independent BPD sample.

2. Material and methods

2.1. Participants

101 unrelated Caucasian patients with BPD (male/female = 15.8/84.2; 34.2 ± 10.4 years old) and 111 ethnically matched healthy controls (male/female = 9.6/90.4; 24.1 ± 7.5 years old) were recruited from a psychiatric department of a French university hospital in Lille. A current diagnosis of BPD was assigned on the basis of the French version of the Structured Clinical Interview for DSM-IV axis-II. Interviews were conducted by trained and experienced raters. DSM-IV axis I disorders were evaluated with the Mini International Neuropsychiatric Interview.

The Mini International Neuropsychiatric Interview (MINI, French version 5.0.0), a standardized psychiatric interview, was used to screen for major psychiatric disorders and substance abuse. BPD patients were not included if at least one of the following criteria was present: (a) dementia or any syndrome with obvious cognitive impairment, (b) doubts in the ability to give informed consent, (c) a current diagnosis of a psychotic disorder, (d) involvement in a legal procedure at the time of study participation, (e) not of Caucasian descent (to reduce genetic heterogeneity of the sample). Control subjects were also assessed for BPD with the personality disorder questionnaire 4+ (PDQ4) (Fossati et al., 1998) and were excluded if BPD or major psychiatric disorders or substance abuse were detected currently or in the past. All participants also filled in the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), a self-administered questionnaire designed to assess traumatic experiences in childhood.

The study was approved by the local ethics committee (CPP Nord-Ouest IV, France). Written documentation of informed consent and capacity to provide consent was obtained from each participant before enrollment.

2.2. Genotyping

Genetic analyses were carried out on saliva samples (Oragene kit,DNA Genotek, Ottawa, ON, Canada), and DNA was extracted using standard methods. Five *FKBP5* SNPs (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) were genotyped using TaqMan SNP genotyping assay (Applied Biosystems, Life Technologies, Thermo Fisher Scientific, Waltham, MA, USA), detected on a real-time PCR DNA Engine OpticonTM 2 system (BIO-RAD, Hercules, CA, USA). Blanks and samples with known *FKBP5* genotypes were taken along as quality controls during genotyping.

2.3. Statistics

Demographic and clinical characteristics of samples were compared for continuous variables using a univariate analysis of variance and categorical data were analyzed using overall Chi-squared (χ^2).

Deviations from Hardy-Weinberg equilibrium (HWE) and pairwise linkage disequilibrium (LD) between all the markers were calculated using Haploview (Version 4.1).

Logistic regression models were used to test the effects of each CTQ subscore (i.e., Physical Abuse, Emotional Neglect, Physical Neglect, Sexual Abuse, Emotional Abuse), FKBP5 genotypes, and their interaction in predicting BPD. Logistic regression models were performed in SAS 9.4.

3. Results

All polymorphisms genotyped were in Hardy-Weinberg equilibrium. Table 1 summarizes the results of the case-control association analyses. All *FKBP5* polymorphisms genotyped showed significant associations with BPD. Haplotype comparisons between BPD and controls showed significant differences in the frequency distribution of *FKBP5* (AAACC; $p = 0.02$) allele combinations (full haplotype data available on request).

In regression models, all childhood trauma exposure showed significant associations with risk of BPD (Supplementary **Tables 1** and **2**). A main effect of rs9470080 ($p = 0.01$) and gene x environment interaction ($p = 0.01$) was found with physical abuse. A gene x environment interaction was also found for rs3800373 ($p = 0.03$) with emotional abuse. None of these interactions remained significant after multiple testing corrections (Bonferroni correction).

4. Discussion

The present results support the hypothesis that genetic variation in the HPA axis genes contributes to BPD susceptibility (Amad et al., 2014; Martín-Blanco et al., 2015). Indeed, in our sample all *FKBP5* polymorphisms genotyped showed significant associations with BPD. Our results confirm the previous study of Marti-Blanco and collaborators who showed that two others *FKBP5* polymorphisms were also associated with BPD (Martín-Blanco et al., 2015). We also found a G x E between two SNPs (rs3800373 and rs9470080) and childhood emotional abuse, even if these results did not remain significant after multiple testing corrections.

FKBP5 is induced following stress exposure via binding of activated GR to several intronic and promoter GR response elements (GREs). The protein itself then binds to the GR complex, reduces the affinity of GR to cortisol and decreases translocation of the GR to the nucleus, providing an ultrashort negative feedback for GR activation on the genomic and protein level (Zannas and Binder, 2014).

FKBP5 has been associated to dysfunctions in HPA axis, both in the general population and in patients with stress-related disorders such as posttraumatic stress disorder (PTSD) (Zannas et al., 2016). Our results might be considered in line with the hypothesis that BPD and PTSD are the two sides of the same coin where one major main key difference could be the age at which trauma occurs (Amad et al., 2016). Indeed, it has recently been proposed that the conceptual interface between BPD and PTSD could be highlighted by the 'age-dependent neuroplasticity' framework which postulates that a same experience. *FKBP5* is thought to be differently regulated according to the different periods of neurodevelopment (Zannas and Binder, 2014) and is also involved in the connectivity of brain regions and circuits related to mood regulation

and cognitive function (Holz et al., 2015). There is also some evidence of age-dependent neuroplasticity following trauma, as it has been showed that the effects of stressors occurring early in development are stronger and more persistent in comparison with stressors occurring during adulthood (Hoffmann and Spengler, 2014).

The present study had several limitations. Firstly, only 5 genetic variants were tested and thus tagging of the *FKBP5* gene was incomplete. Secondly, our sample is small compared to others in the field of psychiatric genetics and therefore does not have the power to identify genome-wide associations. However, candidate studies remain of value and may generate interesting findings and hypothesis. Future studies should include internal replication or larger samples to provide sufficient statistical power to detect small effects, as is the case in collaborative studies.

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Conflicts of interest

None.

Authors' contributions

AA, NR, PT, PG participated in the conception and design of the study; AA and PT participated in the acquisition of data; AA, NR, HP performed the analyses; AA, NR and HP wrote the first draft of the manuscript. All authors participated in the writing and revision of the successive drafts of the manuscript and approved the final version.

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Supplementary materials

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Review article

Similarities between borderline personality disorder and post traumatic stress disorder: Evidence from resting-state meta-analysis

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ABSTRACT

Borderline personality disorder (BPD) and post-traumatic stress disorder (PTSD) are common psychiatric disorders. The nature of the relationship between BPD and PTSD remains controversial, but it has been suggested that these disorders should brought closer because of their many similarities.

We thus performed a quantitative meta-analysis of resting-state functional imaging to assess similarities in the brain activation across BPD and PTSD diagnostic groups.

Overlap analyses revealed decreased activation in the left and right precuneus of both BPD and PTSD groups when compared to control subjects. BPD showed significant increased, but PTSD showed decreased activation, relative to control subjects, in the anterior cingulate/paracingulate gyri and in the left superior frontal gyrus. Complementary overlap analyses on a subgroup of studies with similar sex and age distribution partially confirmed the main results as the same pattern of functional activation in the anterior cingulate and in the left superior frontal gyrus were found.

Our findings are in agreement with the hypothesis that BPD and PTSD share common neuropathological pathways.

1. Introduction

Borderline personality disorder (BPD) is a common mental disorder characterized by a pervasive pattern of emotional lability, impulsivity, interpersonal difficulties, identity disturbances, and disturbed cognition (e.g., depersonalization, derealization, and hallucinations) (Lieb et al., 2004). BPD is estimated to occur in 0.5–5.9% of the general population (Grant et al., 2008; Lenzenweger et al., 2007) and is likely to be diagnosed in early adulthood (Lenzenweger et al., 2007). Follow-up studies show a decrease in impulsivity with age (Stevenson et al., 2003; Zanarini et al., 2007), but associated mood disorders and interpersonal difficulties appear to be persistent and chronic (Zanarini et al., 2007). BPD is commonly comorbid with other psychiatric disorders, notably mood disorders, anxiety disorders, substance abuse, and other personality disorders (Skodol et al., 2002; Tomko et al., 2013).

Post-traumatic stress disorder (PTSD) can develop following exposure to extremely traumatic events (e.g. physical and sexual assaults, accidents, natural disasters). PTSD is characterized by the persistence of intense, distressing, and fearfully avoided reactions to reminders of the triggering event, alteration of mood and cognition, distressing and intrusive memories and nightmares of the trauma, irritability and hypervigilance. PTSD occurs in 5–10% of the population and is also associated with suicidal behaviour (Shalev et al., 2017; Yehuda et al., 2015). Both BPD and PTSD are associated with high mortality and morbidity, due to suicide, frequent hospitalization, substance use, psychiatric comorbidity, considerable economic burden and poor quality of interpersonal relationships (Bisson et al., 2015; Skodol et al., 2002).

The nature of the relationship between BPD and PTSD remains controversial but several arguments suggest that these disorders should

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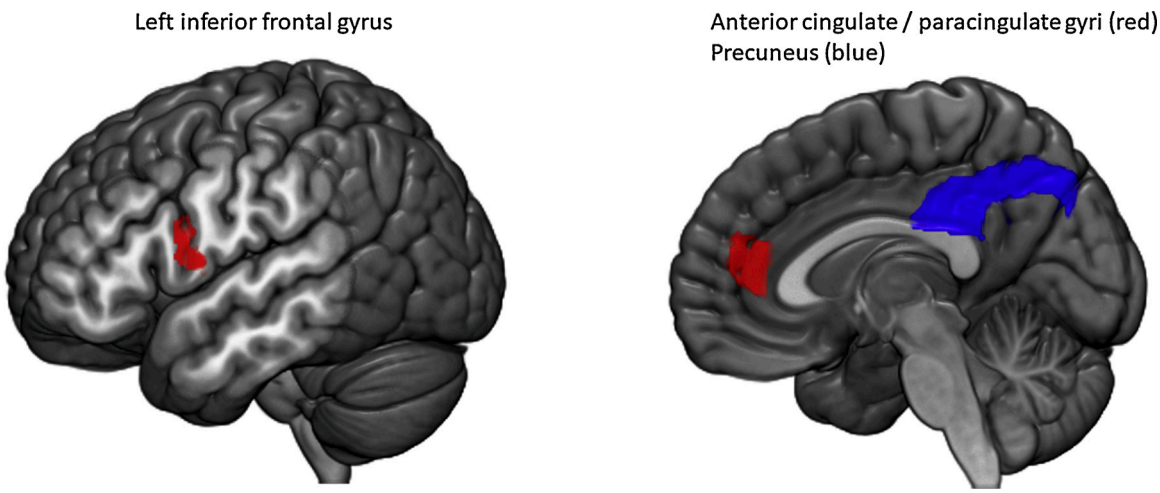

Fig. 1. Regions of increased (red) and decreased (blue) activation at rest in patients with borderline personality disorder compared with healthy controls. Statistical maps are thresholded at $p < 0.005$ and $k > 10$.

brought closer because of their many similarities (Cloitre et al., 2014; Frías and Palma, 2015; Gunderson and Sabo, 1993; Lewis and Grenyer, 2009). First, BPD and PTSD share numerous clinical features, particularly major disturbances in emotional and affect regulation, impulse control, reality testing, interpersonal relationships, self-evaluation and sense of identity (Gunderson and Sabo, 1993; Lewis and Grenyer, 2009; Resick et al., 2012). Second, the role of trauma is obviously essential for PTSD but it also plays a major role in BPD. Indeed, the prevalence of childhood trauma is so frequently associated with BPD (either neglect (92%), sexual abuse (40%–70%) or physical abuse (25%–73%) (Zanarini et al., 2002)) that a causal relationship can be suggested (Ball and Links, 2009). Individuals with BPD are also probably vulnerable to develop PTSD (Golier et al., 2003). Furthermore, recent studies seem to indicate that BPD shares a genetic vulnerability with PTSD as FKBP5 variants − an important functional regulator of the glucocorticoid receptor complex − are associated with PTSD (Zannas and Binder, 2014) − and BPD (Amad et al., 2019; Martín-Blanco et al., 2015), which appears to be consistent with the hypothalamus–pituitary–adrenal (HPA) axis dysregulation highlighted in both disorders (de Kloet et al., 2006; Drews et al., 2019; Schumacher et al., 2019; Wingenfeld et al., 2010). Finally, from a neuro-functional perspective, BPD and PTSD are supposed to share the same abnormalities. Indeed, abnormalities in fronto-limbic networks, particularly a limbic hyperactivity and a diminished recruitment of frontal brain regions, have been suggested for both BPD and PTSD (Krause-Utz et al., 2014; Patel et al., 2012). Interestingly, BPD and PTSD recently showed, in several resting-state functional meta-analysis some common features. Both disorders were associated with an increased activity in inferior and superior frontal gyrus, respectively involved in response inhibition, working memory and attention (Amad and Radua, 2017; Wang et al., 2016). In the same studies, resting-state activation in other regions were found to be differently associated to both disorders such as the anterior cingulate cortex that showed an increased activation in BPD versus healthy controls, but a decreased activation in PTSD versus healthy controls.

To investigate the relationship between BPD and PTSD from a neuro-functional perspective, we performed a functional quantitative meta-analysis to compare results across diagnostic groups and to assess functional similarities that may reflect common neuropathological pathways in these disorders.

2. Material and methods

All brain imaging studies of the resting-state studies which have compared brain activation in patients with BPD or PTSD versus healthy controls were included in two separate meta-analyses (one for BPD and one for PTSD). To identify eligible studies, a systematic search, in respect to the PRISMA statement (Moher et al., 2009), was conducted on the Medline and ISI Web of Knowledge up to April 2018 using the following search term combinations: (1) "neuroimaging", "fMRI", "PET", "ALFF", "ReHo", "rCBF", (2) "resting-state", "default network" and (3) the terms "borderline personality disorder" or "post-traumatic stress disorder". Reviews and meta-analyses were cross-referenced to identify studies that were missed in the literature searches.

Studies were only selected according to the following inclusion criteria: 1) studies were published in an English-language peer-reviewed journal; 2) used at least one of the functional imaging techniques (fMRI, PET, or SPECT), 3) enrolled patients with BPD or PTSD compared to controls, 4) performed a whole brain analysis and reported activation coordinates in standard space (MNI or Talairach), 5) the diagnosis was made according to the current diagnostic criteria for both disorders. Also, we ensured that the same threshold throughout the whole brain was used within each included study, in order to avoid bias toward liberally thresholded brain regions. Authors were contacted for unpublished data including t-maps from the original studies. Article titles and the abstracts of studies identified from the searches were screened and excluded for the following reasons: not written in English, used seed-voxel-based analysis procedures, reported only region of interest results, review article, opinion, or hypothesis article; and samples with a disorder other than BPD or PTSD. The literature search strategy is summarised in the flow chart presented in **S**upplementary Figs. 1 and 2.

The functional neuroimaging meta-analyses were performed using the anisotropic effect size version of Seed-based D Mapping (formerly Signed Differential Mapping, AES-SDM, www.**sdm**project.com) (Radua et al., 2014, 2012). This method allows the inclusion of both peak information (coordinates and t-values) and statistical parametric maps to create whole-brain effect size and variance maps, which are then used to perform voxel-wise random effects meta-analyses.

Peak coordinates and effect-sizes (e.g. t-values or z-scores) of statistically significant differences between patients and controls at the whole-brain level were extracted from each dataset. A standard MNI map of the resting-state differences was then separately recreated for each dataset using an anisotropic Gaussian kernel. The mean map was finally generated by voxel-wise calculation of the random-effects mean of the dataset maps, weighted by the sample size, intra-dataset variability, and between-dataset heterogeneity. All analyses were conducted using the grey matter template included in AES-SDM (template sampling size of 2 × 2x2 mm3 voxels). The default SDM kernel size and thresholds were used (full width at half maximum [FWHM] = 20 mm, $p < 0.005$, peak Z value of > 1, cluster size of > 10). To assess

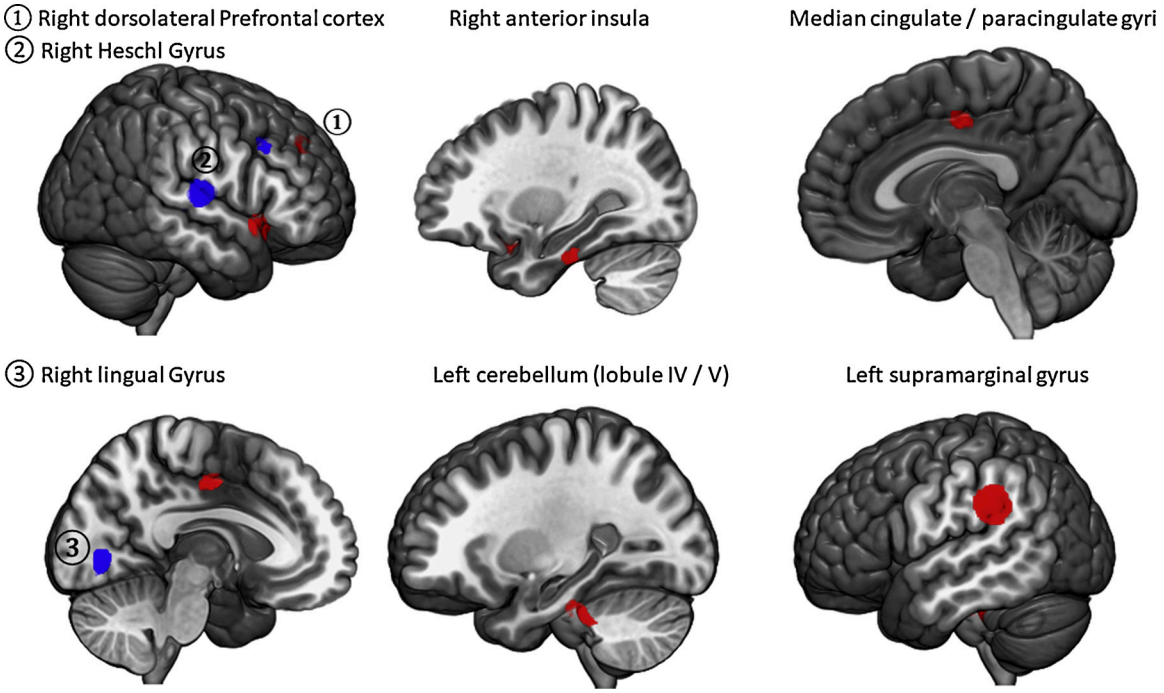

Fig. 2. Regions of increased (red) and decreased (blue) activation at rest in patients with posttraumatic stress disorder compared with healthy controls. Statistical maps are thresholded at $p < 0.005$ and $k > 10$.

heterogeneity between studies, I2 values were extracted from the meta-analytic peaks and interpreted according to (Higgins and Green, 2011). Jackknife sensitivity analyses, consisting of iteratively repeating the meta-analysis excluding one study at a time, were also conducted, for both BPD and PTSD, to examine the robustness of the main meta-analytic output. Meta-regression analyses were performed to study the effects of age and gender. Theses analyses were thresholded more conservatively ($p < 0.0005$) to minimize spurious findings. Publication bias was also examined by using the Egger test.

The multimodal analysis function of the AES-SDM statistical package also allows conjunction analyses to be performed, which enabled us to identify regions where both patient groups show common differences with respect to controls, while taking into account error in the estimation of the magnitude of these differences (Radua et al., 2013). The default parameters of SDM were used (peak $p < 0.00025$, cluster size of > 10).

The main meta-analyses were performed for BPD and all the PTSD studies. Importantly, neural activity abnormalities in patients with PTSD compared to controls can appear dramatically different depending on whether individuals without trauma exposure (non-trauma exposed controls; NTC) or individuals with trauma exposure who did not develop PTSD (trauma-exposed controls; TEC) are employed as experimental controls (Disner et al., 2018). To account for such heterogeneity, the analyses were also performed using, both by merging all the PTSD studies and by performing separate analysis according to the control group. Finally, as BPD and PTSD patients represent different socio-demographic characteristics, especially for age and gender, we conducted a subgroup analysis of studies with similar sex and age distribution (more than half females and mean age less than 40 years).

3. Results

3.1. Studies characteristics

3.1.1. Borderline personality disorder

Nine studies comparing patients and healthy controls (Supplementary Table 1) were included. These studies included a total of 235 patients and 214 healthy controls. Patients' mean age was 28.5 years (SD = 5.3) and 86.5% were female. The mean age of healthy control participants was 30.4 years (SD = 6.3), and 83.6% were female. No information about the history of trauma and its characteristics (age and type) was available.

3.1.2. Post-traumatic stress disorder

Eighteen studies comparing patients and healthy controls (Supplementary Table 2) were included. These studies included a total of 433 patients and 619 healthy controls. Patients' mean age was 39.4 years (SD = 8.78) and 41.3% were female. The mean age of healthy control participants was 40.5 years (SD = 7.8), and 39.4% were female.

3.2. Meta-analysis

3.2.1. BPD vs healthy controls

Functional differences in BPD relative to healthy controls are shown

Table 1
Clusters showing differences between BPD and healthy controls.

MNI coordinates (x, y, z)			SDM-Z	P	Cluster size / voxels	Brodman areas	Side (L/R)	Brain areas
BPD > Controls								
−10	56	22	1.647	0.000304401	805	32	L + R	Anterior cingulate / paracingulate gyri
−54	10	16	1.371	0.002392530	113	44, 48	L	Left inferior frontal gyrus
BPD < Controls								
6	−62	44	−2.268	0.000009835	2043	7	R	Precuneus

Table 2
Clusters showing differences between PTSD and all healthy controls.

MNI coordinates (x, y, z)			SDM-Z	P	Cluster size / voxels	Brodman areas	Side (L/R)	Brain areas
PTSD > Controls								
−56	−38	32	2.346	0.000039041	584	40, 48	L	Supramarginal gyrus
48	20	−10	1.869	0.000604749	437	38	R	Anterior Insula
−26	−28	−30	1.706	0.001354516	166	30	L	Cerebellum (lobule IV / V)
−4	−12	42	1.750	0.001094818	154	23	L + R	Median cingulate / paracingulate gyri
30	−24	−30	1.689	0.001469672	80	20	R	Parahippocampal gyrus
38	42	38	1.999	0.000295222	65	9	R	dlPFC
PTSD < Controls								
40	−20	4	−2.131	0.000078440	1625	48	R	Heschl Gyrus
20	−74	0	−2.202	0.000050783	164		R	Lingual Gyrus
52	22	38	−1.664		35	44	R	Inferior and Middle Frontal Gyri

in Table 1 and Fig. 1.

We found an increased activation in patients with BPD relative to healthy controls in the anterior cingulate, paracingulate gyri and in the left inferior frontal gyrus. Reduced activation was found in the right precuneus. Heterogeneity between studies was substantial in the anterior cingulate cortex (I2 = 63%), moderate in the left inferior gyrus (I2 = 47%) and was not seen in the right precuneus.

3.2.2. PTSD vs healthy controls

Functional differences in PTSD relative to healthy controls are shown in Table 2 and Fig. 2.

We found an increased activation in patients with PTSD relative to healthy controls in the left supramarginal, the right anterior insula, the left cerebellum, the right parahippocampal gyrus, the right dorso-lateral prefrontal cortex (dlPFC) and the median cingulate and paracingulate gyri. Reduced activations in patients with PTSD relative to healthy controls were found in the right Heschl gyrus, the right lingual gyrus and inferior and middle frontal gyri. Heterogeneity between studies was low for all the brain regions found significant (I2 < 25%). The results of the meta-analysis performed by separating the control group in TEC and NTC are detailed in Tables 3 and 4.

3.2.3. Reliability analysis

Jackknife sensitivity analyses showed that the main findings were highly replicable across combinations of datasets for both disorders. Indeed, the increased activity in BPD patients in anterior cingulate cortex and left inferior frontal gyrus were robust as they were significant in all but one combination. Results in the right precuneus were preserved throughout all combinations of the data sets. The activation in patients with PTSD were also highly replicable, being preserved in 16 of 24 combinations of the data sets. See Supplementary Tables 3 and 4 for details.

3.2.4. Age and gender effects

For BPD, meta-regression analysis suggested that a higher percentage of females had significantly increased activation in the left inferior frontal gyrus (MNI coordinates = -44, 42, 10; SDM = 2.697; p < 0.0001, 78 voxels) and in the anterior cingulate (MNI coordinates = 6,44,12 ; SDM = 2.444 ; p < 0.0001; 51 voxels) and a decreased activation the middle occipital gyrus (MNI coordinates = 34,-72,30; SDM = -2.739, p < 0.0001; 726 voxels). Age was associated with an increased activation in the right middle occipital gyrus (MNI coordinates = 34, -72, 32; SDM = 2.802, p < 0.0001, 758 voxels) and a decreased activation in the middle frontal gyrus (MNI coordinates = -44,44,10; SDM = -2.470; p < 0.0001; 172 voxels).

For PTSD, meta-regression analysis suggested that a higher percentage of females had significantly increased activation in the right fusiform gyrus (MNI coordinates = 20,-38,-14; SDM = 6.166; p ˜ 0; 143 voxels) and in the superior temporal gyrus (MNI coordinates = 48,12,-16; SDM = 5.629; p ˜ 0; 109 voxels) and a decrease in the left angular gyrus (MNI coordinates = -42,-62,34; SDM = -5.493; p ˜ 0; 45 voxels). Age was associated with an increased activation in the right supplementary motor area (MNI coordinates = 10,-2,46; SDM = 4.518; p ˜ 0; 1401 voxels) and in the right frontal superior gyrus (MNI coordinates = 22,-2,48; SDM = 2.170; p < 0.0001; 25 voxels) and a decreased activation in the left olfactory cortex (MNI coordinates = -18,4,-14; SDM = -2.018, p < 0.0001; 381 voxels) and in the left lingual gyrus (MNI coordinates = -16,-98,-12; SDM = -1.546; p < 0.0001; 127 voxels).

3.2.5. Publication bias analysis

For BPD, there was no publication bias for these clusters (p-values for Egger tests > 0.15). For PTSD, only the cluster encompassing the dlPFC showed a publication bias (p = 0.003).

3.2.6. Overlap analyses

Overlap analyses (Fig. 3) revealed a significant shared decreased

Table 3
Clusters showing differences between PTSD and trauma exposed controls (TEC).

MNI coordinates (x, y, z)			SDM-Z	P	Cluster size / voxels	Brodman areas	Side (L/R)	Brain areas
PTSD > TEC								
−52	−32	32	2.561	0.000011563	1020		L	Supramarginal Gyrus
0	50	−14	2.180	0.000144601	731	11	L	vmPFC
30	48	32	2.609	0.000008643	386	46	R	dlPFC
58	−54	24	1.665	0.001578987	296	22	R	Angular gyrus
PTSD < TEC								
46	−18	2	−1.759	0.000753582	1111		R	Heschl Gyrus
20	−74	0	−2.897	0.000001013	322		R	Lingual Gyrus
28	−68	−18	−1.629	0.001604378	80	19	R	Cerebellum (lobule VI)
58	2	−26	−1.656	0.001384020	74	21	R	Temporo-parietal Junction
50	22	42	−1.676	0.001234770	46	44	R	Middle Frontal Gyrus
−54	18	30	−1.536	0.002774477	17	44	L	Inferior Frontal Gyrus

Table 4
Clusters showing differences between PTSD and non-trauma exposed controls (NTC).

MNI coordinates (x, y, z)			SDM-Z	P	Cluster size / voxels	Brodman areas	Side (L/R)	Brain areas
PTSD > NTC								
28	−32	−24	2.246	0.000024676	1128	BA 20	Right	Parahippocampal Gyrus
46	20	−6	2.111	0.000076294	703		Right	Anterior Insula
−4	−14	44	1.627	0.001889586	144	BA 23	Left	Median Cingulate / Paracingulate Gyri
−20	−26	−30	1.587	0.002381325	27	30	Left	Cerebellum (lobule IV / V)
0	14	−24	1.518	0.003511727	12	11	Left	Gyrus Rectus
PTSD < NTC								
4	54	−6	−1.664	0.001134872	236	10	Right	vmPFC
46	−76	28	−1.732	0.000762343	144	39	R	Precuneus

activation in both BPD and PTSD groups relative to control subjects in left and right precuneus (MNI coordinates = 0, -46, 38; 606 voxels). BPD showed significant increased, but PTSD decreased activation relative to control subjects in the anterior cingulate/paracingulate gyri and in the left superior frontal gyrus (MNI coordinates = 2, 44, 20; 1205 voxels). The overlap analyses by using specifically TEC or NTC for PTSD studies are presented in Tables 5 and 6.

Complementary overlap analyses were also performed on a subgroup which only included studies with more than half females and a mean age of less than 40 years. Several regions were identified where BPD showed significant increased but PTSD decreased activation relative to control subjects in the anterior cingulate/paracingulate gyri and in the left superior frontal gyrus (MNI coordinates = 2, 38, 0; 506 voxels), but also in the left insula and inferior frontal gyrus (MNI coordinates = -36, 12, 6; 2169 voxels) and in the left hippocampus (MNI coordinates = -26, -8, -24; 340 voxels).

4. Discussion

Here, we report findings from two distinct resting-state functional meta-analyses conducted in BPD and PTSD. For BPD, we found an increased activity in patients relative to healthy controls in the anterior cingulate cortex (ACC) and in the left inferior frontal gyrus, and a reduced activity in the right precuneus, which complements previously published functional meta-analyses using the same method (Amad and Radua, 2017; Visintin et al., 2016). These results contrast with the established fronto-limbic hypothesis of BPD which postulates a decreased activity of frontal brain regions and a limbic hyperactivity. In fact, the brain regions found here may correspond to specific networks involved in pain processing (Kluetsch et al., 2012) and dissociative states (*i.e.* disintegration of perception, consciousness, identity and memory). Dissociation, characterized by subjective detachment from overwhelming emotional experience during and after a trauma, is known to be frequently found (up to two thirds) of BPD patients (Vermetten and Spiegel, 2014). Interestingly, the regions identified here have been associated in participants with PTSD while in dissociative states (Lanius

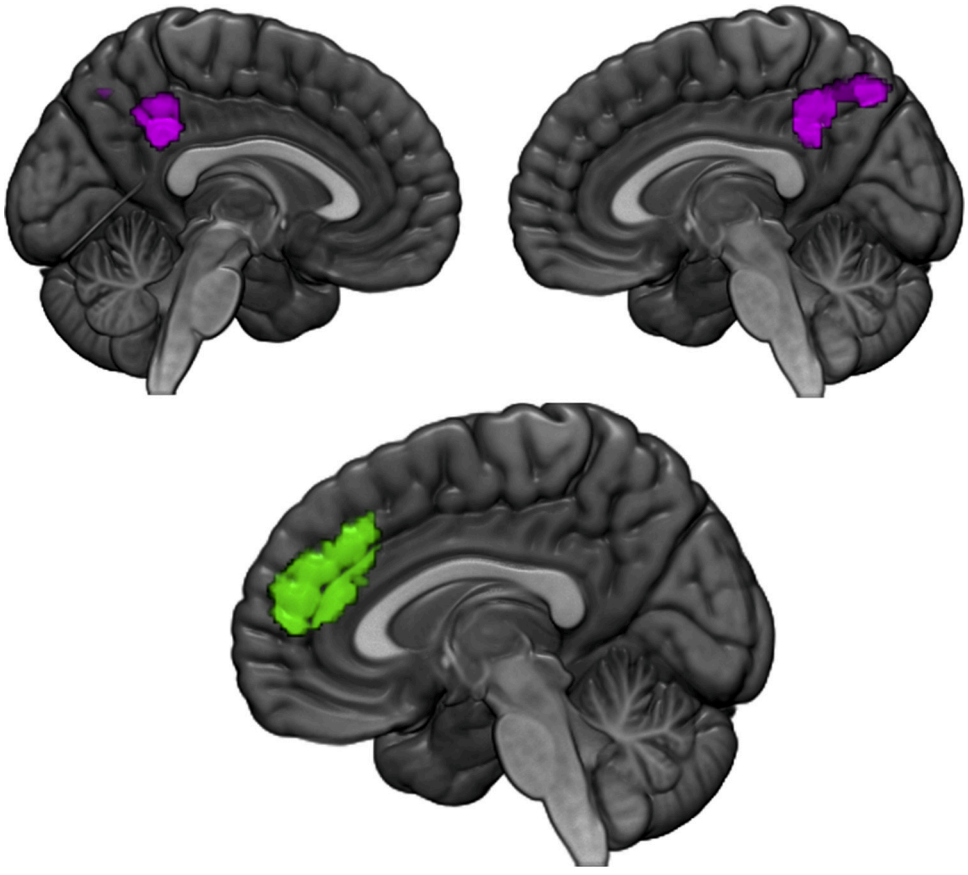

Fig. 3. Clusters showing significant shared decreased activation in both BPD and PTSD (purple) groups relative to control subjects in left and right precuneus (MNI coordinates: 0, -46, 38; 606 voxels). Other regions (in green) were also identified where BPD showed significant increased but PTSD decreased activation relative to control subjects in the anterior cingulate/paracingulate gyri and in the left superior frontal gyrus (MNI coordinates: 2, 44, 20; 1205 voxels).

Table 5
Clusters showing similar activation in BPD and PTSD (trauma exposed controls, TEC).

MNI coordinates (x, y, z)			P	Cluster size / voxels	Brodman areas	Side (L/R)	Brain areas
PTSD pos – bpd pos (increased activity in both ptsd and bpd)							
−46	−6	4	< 0.00025	649	48	L	Left rolandic operculum, Left insula, Left superior temporal gyrus
56	−52	30	< 0.00025	364	39,40	R	Right angular gyrus
PTSD neg – bpd neg (decreased activity in both ptsd and bpd)							
None							
PTSD pos – bpd neg (increased activity in ptsd and decreased in bpd)							
−6	−24	30	< 0.00025	311	23	L + R	median cingulate / paracingulate gyri
PTSD neg – bpd pos (decreased activity in ptsd and increased in bpd)							
−4	58	22	< 0.00025	396	10, 32	L	Left superior frontal gyrus, medial
−24	50	26	< 0.00025	290	46	L	Left middle frontal gyrus, Left superior frontal gyrus, dorsolateral

Table 6
Clusters showing similar activation in BPD and PTSD (non-trauma exposed controls, NTC).

MNI coordinates (x, y, z)			P	Cluster size / voxels	Brodman areas	Side (L/R)	Brain areas
PTSD pos – bpd pos (increased activity in both ptsd and bpd)							
None							
PTSD neg – bpd neg (decreased activity in both ptsd and bpd)							
4	−72	46	< 0.00025	570	7	L + R	Precuneus
PTSD pos – bpd neg (increased activity in ptsd and decreased in bpd)							
24	−28	−14	< 0.00025	834			Right median network, cingulum
−2	−18	30	< 0.00025	440	23	L + R	median cingulate / paracingulate gyri
PTSD neg – bpd pos (decreased activity in ptsd and increased in bpd)							
4	48	4	< 0.00025	827	10, 32	L + R	Right superior frontal gyrus, medial, Left anterior cingulate / paracingulate gyri
−48	−2	2	< 0.00025	608	48	L	Left rolandic operculum

et al., 2002). We also found an increased activity in the left inferior frontal gyrus a critical brain region for response inhibition and for successful implementation of inhibitory control over motor responses (Swick et al., 2008) which has also been associated with attention-deficit/hyperactivity disorder (ADHD) (van Rooij et al., 2015) another disorder characterised by impulsivity and which is often associated with BPD. Finally, one can also suggest that, as several studies about functional neuroimaging findings of emotion processing tasks have shown some evidence of the fronto-limbic hypothesis (Schulze et al., 2016), the resting-state imaging may not be the most accurate modality to demonstrate or refute it.

Regarding PTSD, our results are also highly consistent with a recent resting-state functional meta-analysis using the same method (Wang et al., 2016), even after adding 3 new neuroimaging studies. We found an increased activation in the anterior insula, the cerebellum, the cingulate and paracingulate gyri and the parahippocampal gyrus and a decreased activation in the Heschl and lingual gyri. When the analyses were performed with specific control groups (i.e. NTC or TEC), our results also confirmed previous studies: PTSD patients show (i) increased activation in the anterior insula and decreased activation in the dorso-medial prefrontal cortex when compared with NTC, (ii) increased activation in the ventro-medial prefrontal cortex when compared with TEC (Wang et al., 2016).

In this study, we have also directly compared BPD and PTSD to identify common and distinct patterns of functional modulations. We showed that the two conditions share similar patterns of decreased activation in left and right precuneus. We have also identified that the anterior cingulate/paracingulate gyri and left superior frontal gyrus are affected in both conditions (increased activation for BPD patients and decreased activation for PTSD subjects, relative to control subjects). These results were partially confirmed by complementary analysis on a more homogeneous subgroup regarding age and gender and when the analyses were performed using specific control groups (TEC or NTC).

Reduced activation in precuneus was found in both BPD and PTSD. The precuneus, which is part of the medial parietal cortex, plays a central role to link the limbic structures with parietal regions. This region is also involved in autobiographical memory and in self-referential processing, namely first-person perspective and experience of agency (Cavanna and Trimble, 2006). Precuneus activity has been demonstrated as related to trauma memory generalization (Hayes et al., 2011), and flashbacks (Whalley et al., 2013). Thus, alterations in the precuneus found in BPD and PTSD patients may be related to altered self-referential and memory processes, such as memory deficits, intrusions or flashbacks.

Anterior cingulate/paracingulate gyri and left superior frontal gyrus were also identified to be affected in both conditions. The anterior cingulate gyrus is part of the medial prefrontal cortex (PFC) which exerts inhibitory control over stress responses and emotional reactivity partly through connections with the amygdala. Interestingly, patients with PTSD also exhibit decreased ACC volumes (Bromis et al., 2018), that seem to be consequences of the course of PTSD rather than a pre-existing risk factor (Kasai et al., 2008). Functional imaging studies involving patients with PTSD also found decreased activation of the medial PFC in response to trauma stimuli, such as trauma scripts, combat pictures and sounds, trauma-unrelated negative narratives, fearful faces, emotional stroop (for review see (Sherin and Nemeroff, 2011)). Even if there are discordant findings, reduced activation of the medial PFC was associated with PTSD symptom severity in several studies. Successful SSRI treatment has also been shown to restore medial PFC activation patterns (Shin et al., 2006). Regarding BPD, higher levels of glutamate in the ACC were found in patients when compared with healthy controls, and there are positive correlations between glutamate levels and impulsivity (Hoerst et al., 2010). It has also been shown that the hyperactivation of ACC was correlated with hippocampal activity, abnormal functioning of the memory system, poorer performance in retrieval tasks related to traumatic or emotionally significant memories (Schmahl et al., 2004).

We believe that our results are in line with the hypothesis that the

conceptual interface between BPD and PTSD could be highlighted by the '*age-dependent neuroplasticity*' framework (Amad et al., 2016) which postulates that the same experience can differentially affect the brain plasticity depending on one's age (Kolb and Gibb, 2014). In this perspective, it has then been proposed that trauma during childhood could favour the development of BPD (Amad et al., 2014) while trauma in adulthood could increase the risk of PTSD (Amad et al., 2016). However, this hypothesis could not be tested since no BPD studies included data about the trauma history of these patients. Interestingly, there is a current debate about the distinction between PTSD, BPD and complex PTSD (PTSD plus several symptoms such as emotional dysregulation, negative self-cognitions and interpersonal relationship problems). Complex PTSD has even been recently proposed as a distinct clinical entity in the WHO International Classification of Diseases, 11th version. It has also recently been suggested that the relationship between these three disorders could follow a continuum of trauma and biological severity on a spectrum of common clinical features. These disorders could then be classified together under trauma-related disorders instead of distinct clinical diagnoses (Giourou et al., 2018). However, one of the most frequent, and important, criticism when considering BPD as a trauma spectrum disorder is that the existence of trauma is not necessary or sufficient to explain the development of the disorder (Lewis and Grenyer, 2009).

One of the main limitations of this study corresponds to the very different socio-demographic characteristics of BPD and PTSD patients included, especially for age and gender as highlighted by the meta-regression analysis. Accordingly, we conducted a complementary analysis focusing on studies with more than half females and a mean age of less than 40 years. This complementary analysis partially confirmed our main results as we found the same pattern of functional activation in the ACC and in the left superior frontal gyrus between BPD and PTSD. Another possible limitation is the use of different statistical approaches such as independent component analysis, regional homogeneity, etc. to assess resting-state in the different studies included (Kühn and Gallinat, 2013). As soon as more resting-state studies on BPD and PTSD patients are published, new analysis should be performed including studies with the same statistical approach and future research will also need to confirm our results. Cautious interpretation is also needed because BPD and PTSD have a potentially high clinical heterogeneity and have been associated with many comorbidities, such as depression which can have a significant effect on the resting brain activity (e.g. (Mulders et al., 2015)). Unfortunately, data presented in the different studies included in these meta-analyses did not allow to include these potential confounding factors in our analyses. Our results therefore can hardly be attributed solely to BPD or PTSD. In the same way, no sufficient information about medication was available to perform complementary analysis. Future functional neuroimaging research in this field should directly compare BPD and PTSD patients in studies specifically designed to compare these populations using appropriate paradigms (e.g. task or resting-state). The participants included should be carefully assessed to explore specific dimensions and refined phenotypes (e.g., type and number of trauma, age of exposure, psychotic features or impulsivity). From an epidemiological point of view, the clinical profile of BPD patients with and without a history of childhood abuse could also be directly compared as it seems that the clinical profiles of BPD patients appear to differ according to the severity of childhood trauma (Zanarini et al., 2002). Ideally, these analyses would be performed in large well-characterized epidemiological cohorts powerful enough to detect BPD patients without a history of trauma. Lastly, genetic studies could also help to highlight the similarities/differences between BPD and PTSD, by, for example, comparing shared polygenic risk between these disorders.

In conclusion, this study sheds new light on the neurobiology of BPD, which has been little investigated despite its high prevalence (0.5–5.9% of the general population) and severity (Amad et al., 2014) whilst also highlighting the functional similarities between BPD and PTSD. Our findings help reinforce the hypothesis that BPD shares conceptual and phenomenological similarities with PTSD. One difference between these disorders could be the age at which trauma occurs, differentially affecting the resting brain function and thus the psychiatric symptoms (Amad et al., 2016).

Contributors

AA, JR, TF participated in the conception and design of the study; AA and TF participated in the acquisition of data; AA, JR, TF performed the analyses; AA and TF wrote the first draft of the manuscript. All authors participated in the writing and revision of the successive drafts of the manuscript and approved the final version.

Role of the funding source

No funding source to declare.

Declaration of Competing Interest

The authors declare no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2019.07.018.

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II.Plasticité symptôme dépendante

Dans cette partie nous allons utiliser un autre modèle pathologique permettant d'explorer de nouvelles facettes de la NP. Il s'agit de l'hypothèse de la dysconnectivité de la schizophrénie et de son application à un symptôme spécifique : les hallucinations.

L'hypothèse d'un défaut de connexion entre différentes aires cérébrales dans la schizophrénie est ancienne. Wernicke en son temps, avait déjà élaboré un concept de psychose calqué sur son modèle de l'aphasie. Il s'est en effet servi du modèle neurologique pour expliquer la pathologie psychotique et a introduit le concept de « séjonction » pour expliquer les aphasies, les psychoses et ensuite toute la pathologie mentale (Hulak 2000). Le concept de « séjonction » fait référence à l'interruption de certains faisceaux de fibres reliant des zones cérébrales impliquées dans la psychose (Wernicke 1906).

Plus récemment, des anomalies de connectivité fonctionnelle ont été mises en évidence dans la schizophrénie à l'aide de différents outils d'exploration cérébrale, comme la neurophysiologie (Hoffman et al. 1991) ou la neuroimagerie, permettant d'étudier différents types de connectivité (Figure 3).

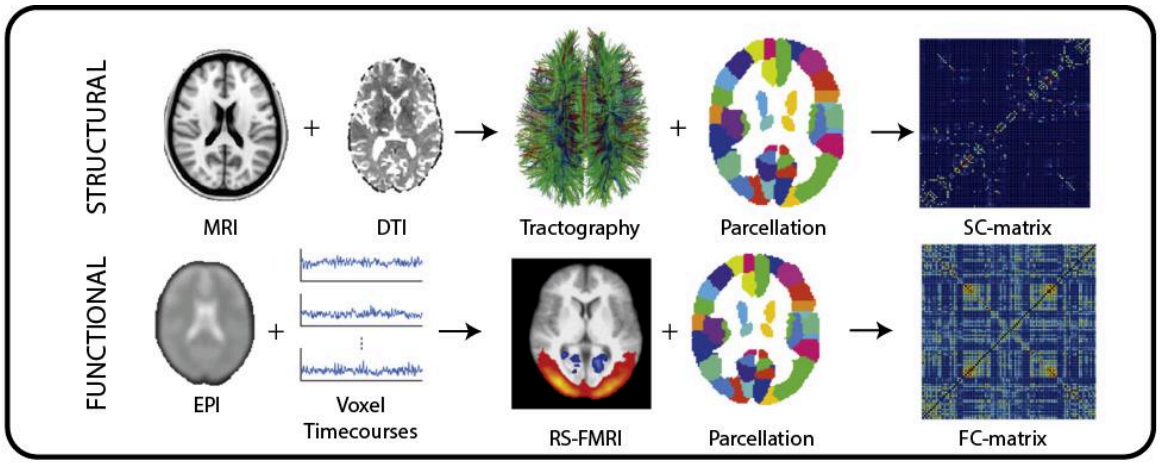

Figure 3 Pour créer un réseau de connectivité structurelle (SC), des données IRM et DTI (imagerie en tenseur de diffusion) sont nécessaires permettant de réaliser des analyses en tractographie pour étudier les liens structurels entre différentes régions grâce à une matrice de connectivité structurelle. Pour créer une matrice de connectivité fonctionnelle, l'activité cérébrale est mesurée ; par exemple l'IRMf à l'état de repos (resting-state), pour enregistrer l'évolution du signal BOLD dans chaque voxel du cerveau. Ces informations, combinées avec un schéma de parcellation cérébrale, sont ensuite utilisées pour recréer l'évolution du signal BOLD (« time course ») dans chaque région d'intérêt. D'après LD Lord (https://ora.ox.ac.uk/objects/uuid:3b6a313c-ad4c-4d09-b423-adb4a56e2031).

Ainsi, nous pouvons citer les travaux précurseurs de Chris Frith et collaborateurs qui montrent que lors de la génération spontanée de mots chez des sujets sains, l'activation frontale est associée à la suppression de l'activité dans le sillon temporal supérieur (STS). A l'inverse, chez des patients schizophrènes chroniques, l'amplitude de l'activation frontale est normale, mais il existe une augmentation importante de l'activation du STS (Frith et al. 1995). Pour expliquer ces observations, Friston propose l'hypothèse de la « *disconnection* » devenue par la suite « *dysconnectivity* » ou dysconnectivité (Friston 1998) impliquant une intégration fonctionnelle anormale entre plusieurs régions cérébrales basée sur une plasticité synaptique anormale dans la schizophrénie (Stephan, Baldeweg, et Friston 2006). L'hypothèse de la dysconnectivité dans la schizophrénie correspondrait donc à un contrôle défectueux de la NP se manifestant par une intégration fonctionnelle anormale des systèmes neuronaux spécialisés (population de neurones, aires corticales…) indispensables aux processus sensorimoteurs et cognitifs.

A l'heure actuelle, différents mécanismes explicatifs de cette dysconnectivité sont proposés. Il pourrait s'agir d'une altération des connexions anatomiques par exemple lors de leur mise en place au cours du développement ou d'anomalies de la NP et de la transmission synaptique (Stephan, Baldeweg, et Friston 2006).Ces mécanismes peuvent bien sûr coexister. En effet, plusieurs arguments, notamment génétiques, appuient l'hypothèse d'un déficit architectural développemental au cours de la mise en place des connexions anatomiques. Plusieurs gènes associés à la schizophrénie sont impliqués dans la mise en place des connexions synaptiques au cours du développement (Le Strat, Ramoz, et Gorwood 2009). Ces anomalies génétique, constitutives, peuvent tout à fait interagir avec des facteurs environnementaux dans une hypothèse d'interaction gène-environnement (Stephan, Friston, et Frith 2009), où des anomalies génétiques entraineraient un défaut au niveau architectural (génétique), auto-entretenu ou facilité par des mécanismes « expérience dépendant » liés à l'influence de l'environnement (Stephan, Baldeweg, et Friston 2006).

En effet, l'environnement joue un rôle crucial dans le développement cérébral. Malgré une large programmation génétique de la différentiation cellulaire, de la migration neuronale et des connexions synaptiques, il existe une régulation fine de ces processus par l'expérience et l'apprentissage. C'est ainsi que la connexion entre deux neurones est fonction de la plasticité synaptique dite « expérience-dépendante » et donc renforcée au plus elle est utilisée (Zhang et Poo 2001). C'est cette force de connexion entre deux neurones qui va déterminer si leur connexion va survivre à « l'élagage développemental » (Hua et Smith 2004).

L'hypothèse de la dysconnectivité peut s'appliquer à des symptômes spécifiques comme les hallucinations. En effet, la complexité (phénotypique, génotypique, neurobiologique) des troubles psychiatriques a stimulé le développement d'outils de caractérisation phénotypique plus fins (endophénotypiques) notamment à travers une approche dimensionnelle. L'approche dimensionnelle permet l'étude des dimensions symptomatiques de la schizophrénie dans le but de réduire l'hétérogénéité clinique de la maladie. Des arguments en faveur du concept de dysconnectivité chez des patients souffrant de schizophrénie présentant des hallucinations auditives ont été apportés par les différentes méthodes d'imagerie.

Les travaux présentés ci-dessous, utilisant différentes méthodes d'imagerie cérébrale, mettent en évidence des arguments en faveur de la dysconnectivité chez des patients souffrant de schizophrénie présentant des hallucinations visuelles. Nous avons aussi montré que cette dysconnectivité est associée à des modifications de la surface du cerveau grâce à des méthodes d'imagerie d'analyses de la morphologie corticale (gyrification/sulcation) correspondant à des marqueurs indirects du développement cérébral d'imagerie structurale. La morphologie corticale et la connectivité cérébrale sont effectivement étroitement liées.

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ORIGINAL ARTICLE

The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations

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Hallucinations constitute one of the most representative and disabling symptoms of schizophrenia. Several Magnetic Resonance Imaging (MRI) findings support the hypothesis that distinct patterns of connectivity, particularly within networks involving the hippocampal complex (HC), could be associated with different hallucinatory modalities. The aim of this study was to investigate HC connectivity as a function of the hallucinatory modality, that is, auditory or visual. Two carefully selected subgroups of schizophrenia patients with only auditory hallucinations (AH) or with audio-visual hallucinations (A + VH) were compared using the following three complementary multimodal MRI methods: resting state functional MRI, diffusion MRI and structural MRI were used to analyze seed-based Functional Connectivity (sb-FC), Tract-Based Spatial Statistics (TBSS) and shape analysis, respectively. Sb-FC was significantly higher between the HC, the medial prefrontal cortex (mPFC) and the caudate nuclei in A + VH patients compared with the AH group. Conversely, AH patients exhibited a higher sb-FC between the HC and the thalamus in comparison with the A + VH group. In the A + VH group, TBSS showed specific higher white matter connectivity in the pathways connecting the HC with visual areas, such as the forceps major and the inferior-fronto-occipital fasciculus than in the AH group. Finally, shape analysis showed localized hippocampal hypertrophy in the A + VH group. Functional results support the fronto-limbic dysconnectivity hypothesis of schizophrenia, while specific structural findings indicate that plastic changes are associated with hallucinations. Together, these results suggest that there are distinct connectivity patterns in patients with schizophrenia that depend on the sensory-modality, with specific involvement of the HC in visual hallucinations.

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Keywords: hallucinations; hippocampus; MRI; neuroplasticity; schizophrenia; visual

INTRODUCTION

Hallucinations can be defined as perceptions in the absence of external stimuli. In schizophrenia, hallucinations constitute the most typical and disabling symptoms of the disorder and may manifest in all sensory modalities. In patients with schizophrenia, hallucinations in the auditory and visual modalities have been described as the most frequent experiences with rates in this population of 60–80%[1] and 24–72%,[2,3] respectively. The neurobiological mechanisms underlying hallucinations remain elusive and complex. Indeed, in comparison with neurological disorders,[4,5] the hallucinations observed in schizophrenia are not related to a focal neurologic dysfunction but rather involves distributed neural networks. A recent coordinate-based meta-analysis[6] of functional imaging studies conducted during auditory hallucinations in patients with schizophrenia demonstrated increased brain activity in speech production and perception areas and in the hippocampal complex (HC; that is, hippocampus and para-hippocampal gyri[7]).

Recent functional and anatomical brain imaging studies on hallucinations suggest that the dysconnectivity hypothesis in schizophrenia[8] could also apply to specific symptoms such as hallucinations.[9] The dysconnectivity hypothesis suggests that the existence of impaired connectivity between different brain regions is responsible for abnormal functional integration within neural networks. This impaired connectivity might be associated with an impaired control of synaptic plasticity.[10–12] The underlying mechanisms for dysconnectivity remain unknown but likely involve both genetic[13] and environmental factors,[14] leading to early alterations in the development of brain wiring and impaired experience-dependent synaptic plasticity.[11]

A proof of concept for dysconnectivity in schizophrenia patients suffering from AH has recently been provided. Functional connectivity (FC), which is based on temporal correlations between the Blood Oxygen Level-Dependent (BOLD) signal in different regions during resting-state functional MRI (fMRI), is altered within the language network of patients with schizophrenia suffering from AH in comparison with non-hallucinating patients or healthy controls.[15,16] No specific FC study has been conducted for nonAH; however, a recent fMRI study of adolescents with a brief psychotic disorder compared with healthy controls were noted to have an increased BOLD signal in modality-dependent associative sensory cortices during AH but also during visual and multisensory hallucinations.[17]

Moreover, white matter connectivity, based on the fractional anisotropy (FA) of diffusion tensor imaging (DTI) signal, is impaired in pathways connecting the perception and production speech

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areas in patients with AH in comparison with non-hallucinating patients or healthy controls.[18–23] An interpretation of variations in FA is not straightforward; however, a reduced FA is commonly interpreted as a loss in white matter integrity,[16,24] whereas an increased FA is thought to reflect an increase in white matter connectivity.[25] Other DTI findings suggest that different hallucinatory sensory modalities are associated with different patterns of anatomical dysconnectivity. For instance, adolescents suffering from early-onset schizophrenia with a history of visual hallucinations exhibit lower FA in the left inferior longitudinal fasciculus, which connects the temporal and occipital cortices, when compared with patients without visual hallucinations.[26] Unfortunately, no other report has specifically assessed brain connectivity in visual hallucinators, despite the significant prevalence of this sensory modality in psychotic experiences.[2,3]

The HC seems to be a key area involved in the pathophysiology of schizophrenia and hallucinations. Indeed, alterations of the hippocampus, a medial temporal formation that is involved in mnesic and neuroplastic processes, have been repeatedly reported in patients with schizophrenia.[27] Such changes include reductions in volume, increases in basal perfusion, activation deficits during declarative memory and reductions in neurogenesis in the dentate gyrus (for a recent review see[27]). In addition, hippocampal hyperactivity has been regularly associated with hallucinations in patients with schizophrenia.[6,28–30] As noted by R-P Behrendt[31], the presence of visual hallucinations, in combination with AH, indicates pathologically increased hippocampal activity. In agreement with this hypothesis, Oertel *et al*.[32] have reported a case of a patient with schizophrenia suffering from visual hallucinations with increased brain activity in cortical visual areas as well as the hippocampus. Finally, electrical stimulation of the HC can produce complex visual hallucinations in epileptic patients.[33]

In this paper, we explored HC connectivity in two subgroups of carefully selected patients with schizophrenia: those with only AH (AH) (that is, patients who never reported visual hallucinations) and those suffering from audio–visual hallucinations (A + VH). The matched subgroups differed only in the presence or absence of visual hallucinations. Such a distinction appears to be crucial in testing for the presence of variable patterns of HC connectivity in hallucinators according to the sensory modality involved. Moreover, this design allows for the assessment of the specific effects of the hallucinatory modality, and expands upon the conventional comparison between patients with schizophrenia and healthy controls. Indeed, specific effects of a hallucinatory modality must be distinguished from effects that are more broadly related to schizophrenia and medication.

We tested for the specific implication of HC in visual hallucinations by exploring the specific patterns of brain connectivity in hallucinators according to the sensory modality involved. Joint multimodal data analysis of HC connectivity, including FC, structural white matter integrity and shape analysis, were used to separately unravel the relationships partially detected by structural and functional measures alone.[34] (1) Functional resting-state connectivity was performed in A + VH and in AH patients. This analysis was seeded on the bilateral HC and we anticipated an increased FC between the HC and specific sensory cortices, that is, the auditory or visual areas, according to the sensory modality involved. (2) FA maps were then compared between A + VH and AH patients. A specific implication of the HC in visual hallucinations was anticipated that could result in a higher structural connectivity between the HC and visual areas in A + VH patients. (3) The hippocampal volumes and shape analyses were finally compared between both groups. This brain area, known capable of experience-dependent plasticity,[35] was considered to be a potential indirect marker of the patterns of connectivity previously explored. On the basis of this hypothesis of the specific role of the hippocampus in visual hallucinations, we expected thicker hippocampi in A + VH schizophrenia patients in comparison with AH patients.

MATERIAL AND METHODS

Participants

Thirty-three outpatients suffering from schizophrenia were included in the study. Of these, there were 17 AH patients and 16 A + VH patients. All participants met the DSM-IV-TR criteria for schizophrenia on the basis of interviews and review of their clinical history by an experienced psychiatrist. The Positive and Negative Syndrome Scale (PANSS)[36] and the Scale for the Assessment of Positive Symptoms (SAPS)[37] were used to evaluate the general psychopathology and to quantify symptomatology. All participants received these semi-structured interviews, which included a detailed assessment of their hallucinatory experiences. All participants were noted to have marked-to-severe AH (SAPS-it. #1 $\geqslant$ 4). Patients from the AH group had never experienced visual hallucinations (that is, SAPS-it. #6 = 0), whereas A + VH patients scored >4 on the SAPS-it. #6. All subjects were otherwise medically healthy and reported no history of head trauma, seizure, neurological disease or significant current major medical condition on the basis of the medical history and medical and neurological examination. None of the patients reported substance abuse with the exception of four patients with the occasional consumption of cannabis (two in AH group and two in A + VH group). No patient with an intelligent quotient <80 was included. Groups were matched for age, sex, handedness, symptom severity, AH and antipsychotic dosage. All patients were being treated with antipsychotic medications at the time of the study (atypical antipsychotics $n = 29$, typical antipsychotics $n = 4$). Olanzapine-equivalent daily doses were calculated in reference to recent international guidelines to assess the homogeneity of antipsychotic dosages across groups.[38] The study was approved by the local ethics committee (CPP Nord-Ouest IV, France). Written documentation of informed consent and capacity to provide consent was obtained from each participant before enrollment.

Procedure, MRI acquisition and preprocessing

Patients underwent multimodal brain imaging, which included structural MRI, fMRI and DTI on a 1.5 Tesla *Intera Achieva* scanner (Philips, The Netherlands). Participants remained still in a state of wakeful rest with their eyes closed. All patients wore headphones and earplugs to attenuate the noise of the scanner. Anatomical and functional data were preprocessed and analyzed using BrainVoyager software (BVQX v2.4, Maastricht, http://www.brainvoyager.com). Preprocessing of DTI included the creation of individual FA images from DTI data using the FMRIB's Diffusion Toolbox, which is a part of FMRIB Software Library (FSL)[39] (FSL 4.1.9, Oxford, www.fmrib.ox.ac.uk/fsl). The detailed MR sequence parameters and preprocessing steps are provided in the Supplementary Methods.

Data analysis

Whole brain analysis

Seed-based functional connectivity (sb-FC). For each subject, correlations between the time-course extracted from *a priori* selected seeds and other brain voxels were computed. Seed regions corresponded to the bilateral HC defined from the ICBM Probabilistic Tissue Atlas (http://www.loni.ucla.edu/ICBM/) (see Supplementary Figure S1). We used the general linear model with z-normalized predictors to obtain individual sb-FC maps. Several nuisance covariates were included in the analyses to reduce the effects of physiological processes such as cardiac and respiratory cycles. Eight covariates of no interest were added to the general linear model: white matter signal, cerebro-spinal fluid signal and head-motion parameters (x/y/z corrections applied in translation and rotation).

After fitting the general linear model and accounting for the effects of temporal serial correlation using AR(2) modeling, a random effects general linear model was conducted for all participants. A group comparison between AH and A + VH patients was then performed using a random-effects analysis of covariance (RFX-ANCOVA). Because VH may be more common in younger adults, age was introduced as a covariate in the analysis.[40]

Tract-based spatial statistics. Tract-Based Spatial Statistics (TBSS),[41] a part of FSL, was used for the voxel-wise statistical analysis of FA map using the standard parameters to study white matter integrity. FA maps were first aligned into a common space using the nonlinear registration tool *FNIRT*,

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which uses a b-spline representation of the registration warp field.[42] Nonlinear transforms obtained from the previous stages were then applied to all subjects to standardize them in the MNI-152 space. The mean FA and mean skeleton (center of all tracts common to the group) were created and thinned. Each subject's aligned FA data were then projected onto this skeleton. An FA threshold of 0.2 was finally applied to limit the cross-subject variability and to restrict the analysis to white matter. Group comparisons were performed using non-parametric permutation tests (randomize function, implemented in FSL). Contrasts between the AH and A + VH groups were on the basis of 10 000 randomized permutations with age introduced as a covariate.

Statistic threshold strategy. Cluster-size thresholding via Monte Carlo simulations[43] was applied to the sb-FC results to correct the statistical maps for multiple comparisons.[44] A *P*-value <0.05 was considered significant. For TBSS, the significance of integrating corrections for multiple pairwise comparisons (*False Discovery Rate*, that is, FDR) was set at $q<0.05$.

Hippocampal volume and shape analysis. FIRST (*FMRIB's Integrated Registration and Segmentation Tool*; part of FSL), a novel analysis technique, was used to segment and measure differences in the volume and shapes of the hippocampus. The left and right hippocampi were automatically segmented from T1-weighted images. Univariate ANCOVA was used to detect group differences in the hippocampal volumes. Hemispheric laterality was included as an independent factor to evaluate the possible interactions between the hallucinatory modality and the hemispheres. Intracranial volume, measured with SIENAX (part of FSL), and age were included as covariates in the analyses. Furthermore, to complementarily investigate a possible lateralization effect of hippocampal volumes, we analyzed the asymmetry index (AI) of the hippocampal volumes, classically computed as AI = (L − R)/(L + R). The hippocampal AI was compared across the two groups using an ANCOVA adjusted for age. For the shape analysis, a surface mesh was created using a Bayesian modeling framework.[45] The number of vertices per mesh was fixed and allowed for point-to-point comparisons across all subjects. After registration to the MNI-152 template, a vertex-wise analysis was performed to compare AH vs A + VH with age introduced as a covariate, thereby providing a local measure of geometric changes in the hippocampi that were dependent on the hallucination's sensory modality. Subregions of the hippocampus were named according to Frisoni's parcellation.[46] The left and right hippocampi were analyzed separately. *P*-values <0.05 were considered statistically significant.

RESULTS

Clinical data analyses are summarized in Table 1 and Supplementary Methods.

Hippocampal complex functional connectivity

Group-level RFX-ANCOVA of HC sb-FC revealed increased connectivity in A + VH patients when compared with the AH group between HC and the *bilateral medial prefrontal cortex* and the *left caudate nucleus* and a decreased sb-FC between HC and the *left lenticular nucleus*, the *right thalamus*, the *superior temporal gyri* and the *right pre-/ post-central gyri* (see Figure 1). Beta-weights averaged over clusters of continuous voxels that achieved significance in the final t-maps were plotted according to the hallucinator group and further validated the RFX-ANCOVA findings (see Supplementary Figure S2). Peak coordinates in the MNI space and the corrected *P*-value ($P_{corr}<0.05$) are reported in Table 2.

TBSS analysis

Due to motion artifacts, only 14 patients from each group were included in the TBSS analysis. Several white matter regions with a significant FA increase were detected in the A + VH group compared with the AH group (see Figure 2). The following tracts connecting the HC to the visual areas were involved: the *right forceps major* (peak MNI x/y/z coordinates (3, − 36,10); $P_{corr}<0.03$), the *right inferior fronto-occipital fasciculus* ((36, − 56,6), $P_{corr}<0.04$), the *left inferior longitudinal fasciculus* ((− 49, − 24, − 18); $P_{corr}<0.04$), the *left cingulum* ((10,42,31); $P_{corr}<0.03$), the *left superior longitudinal fasciculus* ((− 27,33,53); $P_{corr}<0.02$) and the *brainstem* ((− 2, − 26, − 26); $P_{corr}<0.03$).

Hippocampal volume and shape analysis

The hippocampal mean volumes were significantly increased in the A + VH group (left/right hippocampal volumes: 3683.7 mm^3 ± 1356.3/3665.2 mm^3 ± 1203.5 mm^3) compared with the AH group (left/right hippocampal volumes: 2302.7 mm^3 ± 1347.3/2338.3 mm^3 ± 1341.9 mm^3) [$F(1,29)=3.3$, $P<0.01$]. However, neither the hemispheric laterality ($P=0.9$) nor the interaction between hemisphere and hallucinatory modality ($P=0.9$) had an effect on the hippocampal volume. Finally, no group differences were found in the hippocampal AI ($P=0.6$).

Vertex-wise analysis of the hippocampi revealed significant local shape differences in the A + VH group compared with the AH group ($P<0.05$) (See Figure 3). Localized bilateral hypertrophy of the hippocampi on the *anterior* and *posterior end of CA1* and the *subiculum* were detected in the A + VH group when compared with the AH group.

Table 1. Social and clinical characteristics of 33 patients with schizophrenia on the basis of presence of auditory only or audio-visual hallucinations

	Patients with auditory hallucinations (AH)	*Patients with audio-visual hallucinations (A + VH)*	P-*value*
Sample size	17	16	—
Sex (Male/female)	11/6	9/7	0.6
Handedness ratio (right-/left-handed)	16/1	14/2	0.5
Age (mean ± s.d.)	30.47 ± 8.7	30.44 ± 12.6	0.9
PANSS score			
Total (mean ± s.d.)	79.71 ± 21.8	75.64 ± 18.45	0.6
Positive (mean ± s.d.)	19.6 ± 5.1	22.7 ± 4.9	0.1
Negative (mean ± s.d.)	21.29 ± 7.5	17.6 ± 6.5	0.2
General (mean ± s.d.)	38.8 ± 12.2	35.3 ± 9.6	0.4
SAPS score	49.8 ± 19.6	66.5 ± 34.3	0.2
Item 1 (mean ± s.d.)	4.7 ± 0.6	4.8 ± 0.5	0.9
Item 6 (mean ± s.d.)	0	4.5 ± 0.5	< 0.0001
Olanzapine equivalent dose (mean ± s.d.)	23.7 ± 7.8	20.57 ± 15.0	0.4

Abbreviations: AH, auditory hallucinations; A + VH, audio visual hallucinations; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms.

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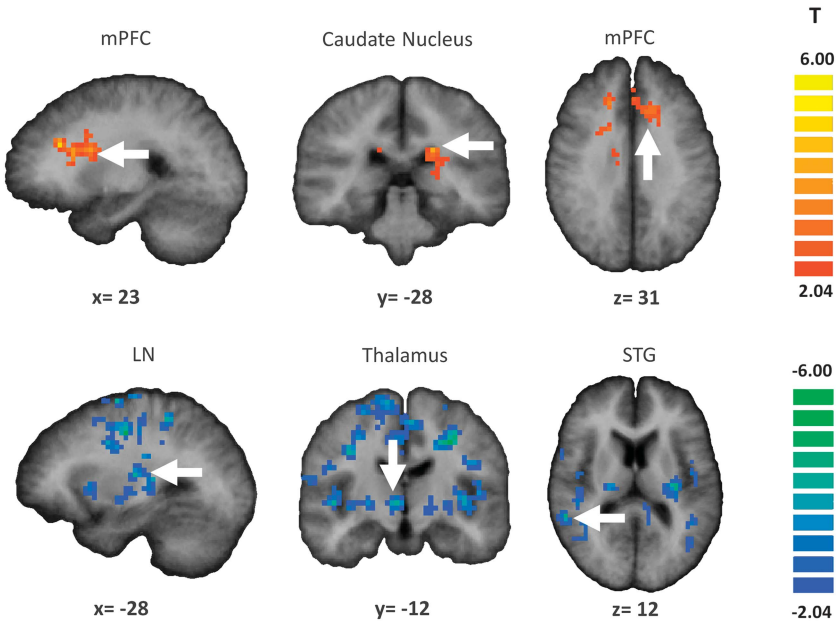

Figure 1. Whole-brain voxel-based comparisons of the hippocampal functional connectivity in schizophrenia patients with auditory-only (AH, $n = 17$) or audio-visual (A + VH, $n = 16$) hallucinations. The left and right hippocampal complexes (HCs) were defined as regions-of-interest for the seed-based functional connectivity analysis (sb-FC, See Supplementary Figure S1). Contrast maps are overlaid on a spatially normalized averaged MRI brain ($n = 33$; $P_{corr} < 0.05$). Increased sb-FC was detected in A + VH patients within the bilateral medial prefrontal cortices (mPFC) and the left caudate nucleus (upper panel). A decreased sb-FC was measured in A + VH patients within the left lenticular nucleus, the right thalamus and the superior temporal gyri (lower panel).

Table 2. Differential functional connectivity (FC) of the hippocampal complex between the following two groups of schizophrenia participants: patients with audio-visual (A + VH, $n = 16$) or auditory (AH, $n = 17$) hallucinations

Brain area	*Side (L/R)*	*BA*	*MNI coordinates*			*Cluster size (mm^3)*	*$t_{max}(30)$*	*P_{corr}value*
			x	*y*	*z*			
A + VH > AH								
Medial prefrontal cortex	R	9	26	34	19	3687	5.19	< 0.0001
	L	9	0	44	28	5647	5.06	< 0.0001
Caudate nucleus	L	—	− 19	− 24	25	2720	6.96	< 0.0001
AH > A + VH								
Precentral gyrus	R	6	56	1	30	12 069	− 4.75	< 0.0001
Superior temporal gyrus	R	22	59	− 40	12	4536	− 4.71	< 0.0001
Postcentral gyrus	R	2	63	− 19	38	4995	− 4.50	< 0.0001
Middle frontal gyrus	L	6	− 29	− 7	39	65 664	− 5.89	< 0.0001
Thalamus (medial dorsal nucleus)	R	—	8	− 11	1	3564	− 4.46	= 0.0001

Abbreviations: AH, auditory hallucinations; A + VH, audio visual hallucinations.
Correction for multiple comparisons was performed using Monte Carlo simulations at the cluster level. Note: BA = Brodmann areas; L/R = left/ right side of the brain.

DISCUSSION

The current study is the first to report the differential involvement of HC connectivity in a manner dependent on the sensory-modality involved in the hallucinations of patients with schizophrenia. On sb-FC analysis, patients with auditory-only hallucinations exhibited a higher sb-FC between the HC and the thalamus in comparison with the A + VH group. Furthermore, increased FC of the HC with the medial prefrontal cortex and caudate nuclei was noted in the A + VH group when compared with the AH group. These regions belong to the hippocampo-prefrontal pathway, which originates from the CA1/subiculum hippocampal sub-fields and projects onto the medial prefrontal cortex and the ventral striatum.[47] These structures send projections to the ventral tegmental area, a dopamine projection system that projects to the cortex.[47] Previous research has already suggested that presynaptic striatal dopaminergic function correlates with the severity of positive symptoms.[48] However, the exact relationship between dopaminergic function and hallucinations remains unknown. Only one study specifically examined this relationship and compared healthy individuals with frequent auditory verbal hallucinations ($n = 16$) to matched controls.[49] Even if this study failed to report group differences in dopamine synthesis capacity, current findings are consistent with the idea that in schizophrenia, an increased dopaminergic transmission may lead to more complex hallucinatory experiences (that is, one supplementary sensory modality in A + VH patients).

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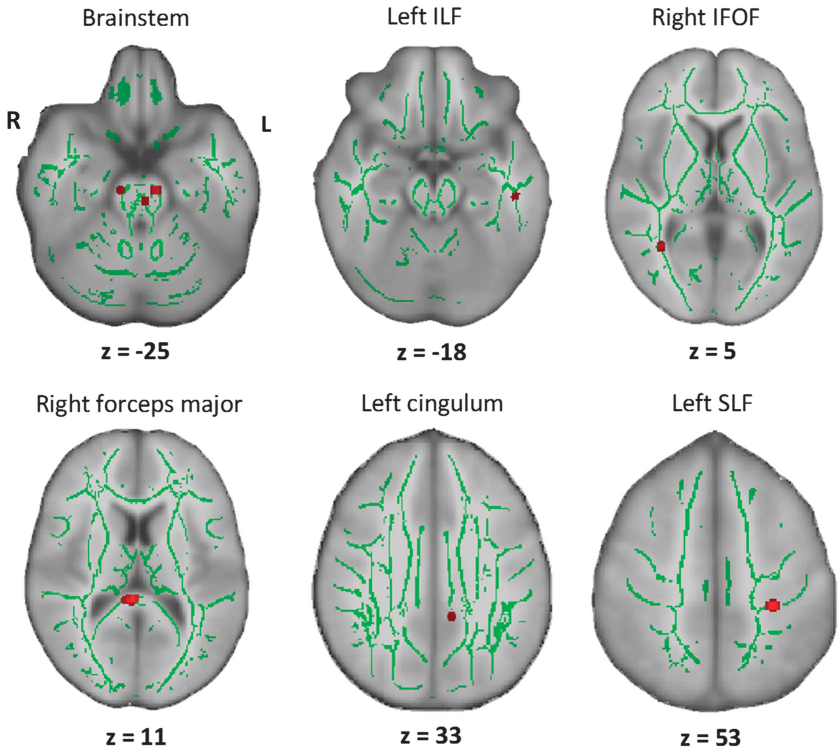

Figure 2. Tract-Based Spatial Statistics (TBSS) between schizophrenia patients with audio-visual (A + VH, $n = 14$) and auditory (AH, $n = 14$) hallucinations. TBSS results are overlaid on the MNI-152 template with the mean FA skeleton (green) ($n = 28$; $P_{corr} < 0.05$). Red clusters indicate white matter regions with increased fractional anisotropy in A + VH patients compared with AH patients: three clusters in the brainstem (x,y,z MNI coordinates: (−9, −20, −26)/ (−2, −26, −26)/ (12, −20, −27)); ILF: inferior longitudinal fasciculus (−49, −24, −18); IFOF: inferior fronto-occipital fasciculus (36, −56,6); forceps major (3, −36,10); cingulum (−10, −42,31); SLF: superior longitudinal fasciculus (−27, −33,53). R/L: right/left side of the brain. The TBSS-fill script was used to improve the visualization of the results.

Interestingly, some authors have already suggested that AH may be regarded as 'underconstrained' perceptions that arise when the impact of sensory input on the activation of thalamocortical circuits and synchronization of thalamocortical gamma activity is reduced.[31] The current findings fit particularly well with such a theory; this relationship is reinforced by the fact that the frontal and temporal regions, which are anatomically connected to the thalamus[50] through the lentiform nucleus,[51] were strongly functionally connected with the HC in AH patients. Of note, all of these regions, which are crucial for language processing,[52] were previously shown to be activated, together with the pre- and post-central gyri, during AH in both psychotic and nonpsychotic subjects.[53] In addition, we confirmed that the particular FC patterns measured here were specific to the sensory modality involved in hallucinatory experiences, (that is, AH or A + VH) rather than the underlying disorder (that is, schizophrenia), which is common to both groups. Together, our results suggest that the HC is an essential relay within the neural networks involved in hallucinatory phenomena and is differentially connected to cortical–subcortical areas on the basis of the hallucinatory modality.

This study also compared white matter structural connectivity between patients with auditory and audio-visual hallucinations. TBSS analyses revealed that most of the white matter tracts with significantly increased FA in A + VH patients connected the HC to visual areas. These bundles included the forceps major, an extension of the splenium that links the bilateral occipital lobes. Of note, the portion of the forceps major that had a significant FA increase was precisely the portion connected to the right hippocampus.[54,55] The other bundles that had significant FA increases included the right inferior fronto-occipital fasciculus, the left inferior longitudinal fasciculus (which joins the occipital lobe to the para-hippocampal gyri[56]), the left cingulum (which connects the frontal lobe with the HC) and the left superior longitudinal fasciculus (which is composed of four separate components, most of which originate from the occipito-parietal region[57]). Thus, TBSS analysis confirmed that the HC was not only linked to the phenomenon of hallucinations in schizophrenia but seemed specifically involved in visual hallucinations.

Finally, volume and shape analysis of the hippocampus revealed hypertrophy in the A + VH group localized at the level of the CA1 and the subiculum subfields. These local volumetric differences may rely on plastic modifications of the hippocampus. More specifically, these plastic changes could be related to the specific hippocampal 'connectome', that is, the feed-forward connectivity with the striatum and the prefrontal cortex and the feedback connectivity with visual areas[58] (connections that were both noted to be increased in A + VH patients). Indeed, the hippocampus is capable of plastic deformation,[59] and the present findings are consistent with experience-dependent shape modifications of the hippocampus that involve mechanical tension along the axon.[60] This hypothesis fits nicely with the global dysconnectivity hypothesis stating that it is not plasticity *per se* that is abnormal but its modulation during reinforcement[11] and its neurobiological regulation.

A recent study reported shape modifications of the hippocampal subfields in patients with schizophrenia.[61] Although this last study did not specifically question the role of hallucinations in the shape of hippocampal subfields, a surface inward deformation was measured at the level of the anterior hippocampi when comparing patients with schizophrenia to healthy controls and may underlie the impaired performances observed in hippocampal-dependent memory tasks.[61] Moreover, a negative correlation has recently been shown between the PANSS-positive

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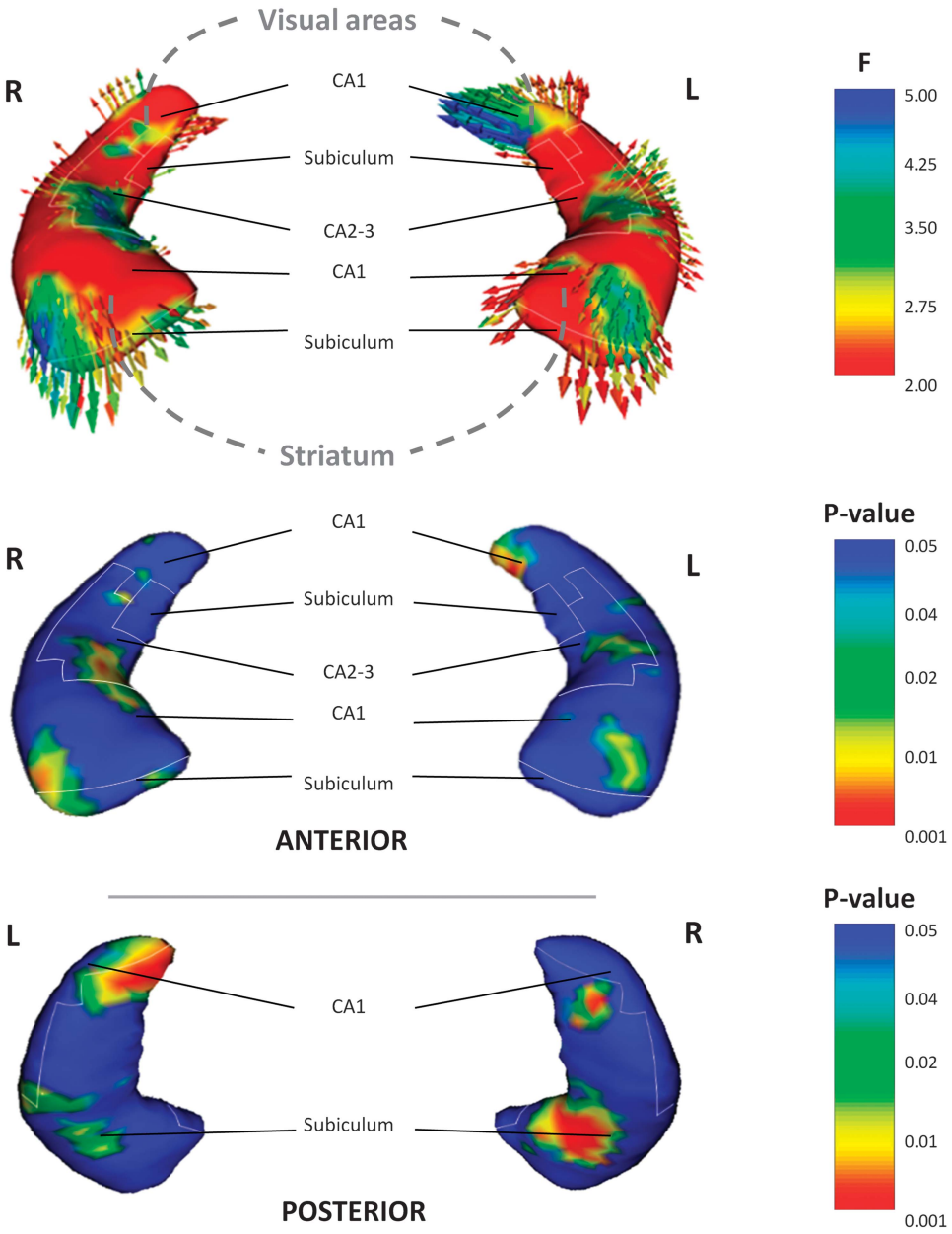

Figure 3. Local hippocampal shape differences in schizophrenia patients with auditory-only (AH, $n = 17$) or audio-visual (A + VH, $n = 16$) hallucinations. Upper panel: vertex-wise analysis revealed localized hypertrophy of the bilateral hippocampi (vectors pointing outward) in A + VH-patients compared with AH-patients ($n = 33$; $P < 0.05$). Middle and lower panels: *P*-value maps overlaid on segmented hippocampi 3D surfaces indicate local differences between the two groups (anterior and posterior views). R/L: right/left side of the brain; CA: cornu ammonis.

subscale and volumes of the bilateral hippocampal subfields (CA1/2/3). This finding reinforces our hypothesis of subfield dysfunction, which is commonly involved in sensory representations, resulting in positive symptoms such as hallucinations.[62] Interestingly, the posterior hyper-connectivity of the hippocampus with visual areas, as evidenced in the current study, suggests a specific pattern of visual hallucinations that are independent of the diagnosis of schizophrenia. The focus on the specific hallucinatory modality in our analysis thus allowed us to clarify the involvement of the hippocampus in the positive symptoms of schizophrenia.

The moderate sample size used in this experiment should be acknowledged. However, the high-group homogeneity allowed us to address strong *a priori* hypotheses and draw significant conclusions. Computing power for fMRI and connectivity studies remains complex, and there is no widely applied standard approach. Combining two matched samples of more than 15 subjects each was recently judged to be adequate[63] in such a context, and this adequacy appears to be reinforced by the use of a multimodal design that provides convergent findings. Another point of discussion concerns the use of customized templates to improve the registration quality across MRI modalities and patients. Spatial normalization in the MNI/Talairach space is a standard and validated approach that is commonly used for group comparisons on the entire brain. The use of customized templates generated from the tested population—as enabled for instance by DARTEL algorithm for structural MRI[64]—has been proposed as an interesting alternative to the MNI/Talairach template. Such an approach has been shown to be particularly well adapted in the context of brain morphometry.[65,66] A similar non-linear registration with a customized template was used here for TBSS

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analysis. However, in the case of fMRI data, such approaches can be considered to be of more limited interest,[67] most likely because of the lower spatial resolution of the functional data compared with the structural data (here, 4 mm^3 of voxel size on which was applied a 5 mm FWHM spatial smoothing). Hence, even if a false negative cannot be fully excluded in the current study because of sensitivity issues (in particular for the fMRI analysis), the likelihood that the spatial normalization steps might have resulted in a false positive is considered to be low.

To summarize, the use of different imaging techniques in the present study provided complementary and novel results. The functional findings are consistent with the fronto-limbic dysconnectivity hypothesis of schizophrenia, thus implicating multiple interactions between the prefrontal cortex, thalamus and striatum that are modulated by midbrain dopaminergic neurons and have a central role in basic information processing and positive symptoms.[68] Second, structural findings support plastic abnormalities that are associated with hallucinations rather than with the underlying mental disorder. These findings are consistent with recent research that considers gray matter reductions within the language network of patients with AH to be plastic adaptations related to the hallucinations themselves[69,70] and extends them to other sensory modalities. On the basis of these findings, we would like to defend the idea that the neuroplastic framework could provide a unifying model for modality-dependent hallucinations, which encompass the many gene interactions and neurotransmitters that are involved in schizophrenia, such as glutamate, dopamine, GABA and acetylcholine.[71] For instance, several serotoninergic and dopaminergic genes are associated with hallucinations in patients with schizophrenia and could be considered to be 'plasticity genes' rather than 'vulnerability genes,' which for better or worse, make patients more susceptible to environmental influences.[72]

The importance of neuroplasticity in hallucinations is finally reinforced by observations of the brain impact of neuromodulation techniques used to relieve drug-resistant hallucinations. Repetitive transcranial magnetic stimulation, a noninvasive and painless technique currently used for this indication,[73] induces neuroplastic changes and modifications of the FC of the temporo-parietal junction, a target chosen for its involvement in AH.[74,75] Current findings fully support the future development of therapeutic strategies to address extra-AH on the basis of the neuro-guided repetitive transcranial magnetic stimulation, which could modulate the connection strength of specific neural networks, such as the networks identified in the present study (for example, testing for distant effects on the HC when treating visual hallucinations). Future research will also need to confirm the impact of multimodal MRI guidance as a promising tool for the personalized therapy of refractory complex hallucinations.

In conclusion, both the strength and reliability of the findings rely on the highly selected and homogeneous samples, as well as the use of three complementary brain imaging approaches (sb-FC, TBSS and shape analysis). By focusing on the presence or absence of visual hallucinations in schizophrenia patients suffering from AH, we unraveled specific patterns of hippocampal connectivity and proposed a refined pathophysiological model for modality-dependent hallucinations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

All the authors designed the study; AA, PT, DP, RJ recruited the participants; CD, DP, RJ acquired the MRI data; AA, AC, RJ performed the analyses. All the authors contributed to the manuscript writing.

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ORIGINAL ARTICLE

Deviations in cortex sulcation associated with visual hallucinations in schizophrenia

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Hallucinations, and auditory hallucinations (AH) in particular, constitute the most typical and disabling schizophrenia symptoms. Although visual hallucinations (VH) have been largely neglected in psychiatric disorders, a recent review reported a 27% mean prevalence of VH in schizophrenia patients. The pathophysiology underlying VH in schizophrenia remains elusive. Several schizophrenia studies reported a significant effect of age on VH; therefore, we tested the hypothesis that the neurodevelopmental model of schizophrenia may explain VH occurrence. We analyzed cortex sulcation, a marker of brain development, in healthy controls (HCs) and two subgroups of carefully selected schizophrenia patients suffering from hallucinations: patients with only AH (that is, patients who never reported VH) and patients with audio–visual hallucinations (A+VH). Different cortical sulcation and left–right sulcal asymmetry were found between A+VH and AH patients, with decreased sulcation in both A+VH and AH patients in comparison with the HCs. Although a specific association between VH and neurodegenerative mechanisms, for example, in Body-Lewy Dementia or Parkinson's Disease, has previously been reported in the literature, the current study provides the first neuroimaging evidence of an association between VH and neurodevelopmental mechanisms.

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INTRODUCTION

Hallucinations constitute the most typical and disabling symptoms of schizophrenia and may manifest in all sensory modalities.[1] In patients with schizophrenia, auditory hallucinations (AH) have been described as the most frequent experiences, with occurrence rates of 60–80%.[2] Although visual hallucinations (VH), defined as erroneous visual perceptions not elicited by an external stimulus, have been largely neglected in psychiatric disorders, a recent literature review evidenced a weighted mean VH of 27% in schizophrenia,[3] ranging from 24 to 72%.[4,5] Several phenomenological properties of VH may differ according to the underlying diagnosis (that is, psychotic disorders vs neurological disorders), including frightening content, emotional reactions and appraisals of personal significance. In contrast to what can be observed in neurological disorders or eye diseases,[3] schizophrenia is characterized by VH typically co-occurring with hallucinations in other sensory modalities.[5–8] It has been reported that VH and AH co-occur in up to 84% of individuals with schizophrenia,[7] whereas for other authors, VH were considered to never occur in isolation in schizophrenia patients.[8]

The pathophysiology and pathogenesis of the underlying hallucinations in schizophrenia remains elusive and complex. Indeed, in comparison with neurological disorders, hallucinations observed in schizophrenia are not related to focal neurological dysfunctions, but rather involve impaired neural networks with distributed regional abnormalities and connectivity disruptions.[9] We recently reported distinct anatomical and functional connectivity in schizophrenia patients with pure AH compared with patients with audio–visual hallucinations (A+VH).[10] In addition, the pathogenesis of hallucinations may benefit from the neurodevelopmental hypothesis of schizophrenia, which posits that the disorder is the end state of abnormal neurodevelopmental processes that started years before the onset of the illness.[11] Indeed, analyses of the cortex morphology in schizophrenia patients reported sulcal differences, markers of early brain development deviations,[12] that have been shown to be associated with AH.[13–15] Surprisingly, no brain imaging studies have investigated the neurodevelopmental processes associated with VH in schizophrenia, even though several studies reported a significant effect of age on this symptom, based on the more common occurrence of VH in younger patients with schizophrenia.[16,17] A recent study conducted on childhood-onset schizophrenia also suggested that VH could be considered a severity index of neurodevelopmental abnormalities.[18] In addition, several studies reported that the rate of VH in schizophrenia was age-dependent.[19]

In this context, the present study was aimed at testing the hypothesis of neurodevelopmental deviations associated with VH in schizophrenia. We compared healthy controls with two subgroups of carefully selected schizophrenia patients with hallucinations: patients with only AH (that is, patients who never reported visual hallucinations) and patients suffering from A+VH. The matched subgroups of patients differed only in the presence or absence of VH. Such a distinction appeared crucial in testing for variable cortical sulcation in hallucinators according to the sensory modality involved.

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MATERIALS AND METHODS

Participants

Forty-nine participants were included in the study, including 33 out-patients suffering from schizophrenia[10] and 16 healthy controls (HC) with no personal history of psychiatric disorder or family history of psychosis. Of the 33 patients, there were 17 AH patients and 16 A+VH patients. All patients met the DSM-IV-TR criteria for schizophrenia based on interviews and review of their clinical history by an experienced psychiatrist. The Positive and Negative Syndrome Scale (PANSS)[20] and the Scale for the Assessment of Positive Symptoms[21] were used to evaluate general psychopathology and to quantify symptomatology. All the patients received these semi-structured interviews, which included a detailed assessment of their lifetime hallucinatory experiences. All the patients were noted to have marked-to-severe auditory hallucinations (Scale for the Assessment of Positive Symptoms-it. #1 $\geqslant 4$). Patients from the AH group had never experienced visual hallucinations (that is, Scale for the Assessment of Positive Symptoms-it. #6 $=0$), whereas A+VH patients scored greater than 4 on the Scale for the Assessment of Positive Symptoms-it. #6. All the subjects were otherwise medically healthy and reported no history of head trauma, seizure, neurological disease or significant current major medical condition based on medical history and medical and neurological examination. None of the patients reported substance abuse, with the exception of four patients reporting the occasional consumption of cannabis (two in AH group and two in A+VH group). No patient with an intelligence quotient below 80 was included. Groups were matched for age, sex and handedness (all $P > 0.7$); AH and A+VH patient groups were also matched for symptom severity, auditory hallucinations and antipsychotic dosage (Table 1). Group-matching on age and gender notably allows controlling for potential confounding effects on sulcal anatomy as reported before.[13,22] All the patients were being treated with antipsychotic medications at the time of the study (atypical antipsychotics $n = 29$, typical antipsychotics $n = 4$). Olanzapine-equivalent daily doses were calculated in reference to recent international guidelines to assess the homogeneity of antipsychotic dosages across groups.[23] The study was approved by the local ethics committee (CPP Nord-Ouest IV, France). Written documentation of informed consent and capacity to provide consent was obtained from each participant prior to enrollment. Clinical data analyses are summarized in Table 1.

MRI acquisition

All participants underwent a 10-min anatomical T1-weighted sequence (three-dimensional multi-shot turbo-field-echo scan; 150 transverse slices, field of view = 256 mm^2 and voxel size = 1 mm^3) on a 1.5 Tesla Intera Achieva scanner (Philips, Best, The Netherlands). All subjects wore headphones and earplugs to attenuate the noise of the scanner. These magnetic resonance imaging (MRIs) were adapted to the reconstruction of the fine individual cortical folds.[13]

Measure of cortex sulcation

To assess the cortex morphology at both global and regional levels, the raw MRI data were subjected to automatized estimation of three-dimensional surface-based sulcus areas by means of a three-step procedure.[13] This approach has been previously applied in the investigation of cortical folding abnormalities in patients with schizophrenia[13,24,25] and bipolar disorder.[26,27] Image analysis was performed with the Morphologist toolbox using BrainVISA 4.2 software with standard parameters (http://brainvisa.info/).

First, an automated pre-processing step skull-stripped T1 MRI and segmented the brain tissues (cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM)) and calculated, in each hemisphere, the total intracranial volume (= GM + WM + CSF volumes) and the area of the outer cortex from non-normalized images. The hemispheric outer cortex area was defined as the area of a smooth envelope of the brain mask that wrapped around the hemisphere but did not encroach into sulci. The envelope was obtained with a morphological closing of the brain mask; an isotropic closing of 5 mm was used to ensure boundary smoothness. The cortical folds were then automatically segmented throughout the cortex from the skeleton of the GM/CSF mask (see Figure 1), with the cortical folds corresponding to the crevasse bottoms of the 'landscape', the altitude of which is defined by intensity on the MRI. This definition provides a stable and robust sulcal surface definition that is not affected by variations in the cortical thickness or span, as well as the GM/WM contrast.[28] The cortical folds were then converted to a graph-based representation of the cortex containing information related to shape (area, depth and length) and spatial organization (position and orientation). No spatial normalization was applied to the MRI data to overcome potential bias because of the sulcus shape deformations induced by the warping process.

Second, the area of each cortical fold was computed as the sum of all of the triangular areas defining the fold mesh. The global sulcal index (g-SI) for each hemisphere was measured as the ratio between the total sulcal area (that is, the sum of the areas of all segmented cortical folds) and the total outer cortex area (Figure 1a and c):

$$g-SI^{hemisphere} = \frac{\sum_{sulcus \in hemisphere} A_{sulcus}}{A_{brain\ hull}{}^{hemisphere}}$$

(with A_{sulcus}, the sulcus surface area and $A_{brain\ hull}{}^{hemisphere}$, the brain hull area).

A cortex with extensive folding has a large g-SI, whereas a cortex with low degree of folding has a small g-SI (Figure 1d). At a constant outer cortex area, the g-SI increases with the number and/or area of sulcal folds, whereas the g-SI of a lissencephalic cortex is zero. G-SI describes the burying of the cortex and is therefore slightly different from the classical gyrification index, the ratio of the whole gyral contour length to the outer,

Table 1. Demographical and clinical characteristics of the 49 participants enrolled in the study (33 patients with schizophrenia based on the presence of auditory only or audio–visual hallucinations, and 16 healthy controls)

	Healthy control	*Patients with auditory hallucinations*	*Patients with audio–visual hallucinations*	*AH vs A+VH (P-value)*
Sample size	16	17	16	—
Sex (male/female)	10/7	11/6	9/7	0.6
Handedness ratio (right-/left-handed)	16/1	16/1	14/2	0.5
Age (mean ± s.d.)	29.93 ± 5.2	30.47 ± 8.7	30.44 ± 12.6	0.9
PANSS score				
Total (mean ± s.d.)	—	79.71 ± 21.8	75.64 ± 18.45	0.6
Positive (mean ± s.d.)	—	19.6 ± 5.1	22.7 ± 4.9	0.1
Negative (mean ± s.d.)	—	21.29 ± 7.5	17.6 ± 6.5	0.2
General (mean ± s.d.)	—	38.8 ± 12.2	35.3 ± 9.6	0.4
SAPS score		49.8 ± 19.6	66.5 ± 34.3	0.2
Item 1 (mean ± s.d.)	—	4.7 ± 0.6	4.8 ± 0.5	0.9
Item 6 (mean ± s.d.)	—	0	4.5 ± 0.5	< 0.0001
Olanzapine-equivalent dose (mean ± s.d.)	—	23.7 ± 7.8	20.57 ± 15.0	0.4

Abbreviations: AH, auditory hallucination; A+VH, audio–visual hallucinations; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms. Quantitative (resp. qualitative) demographic and clinical characteristics comparisons between groups were based on bilateral Student's *t*- (resp. X^2-) tests.

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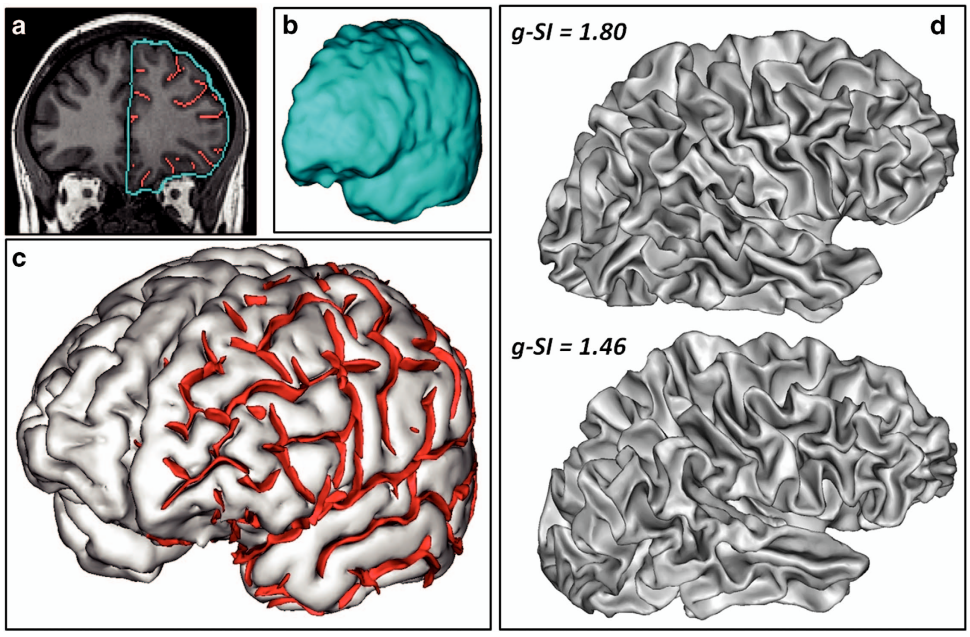

Figure 1. Three-dimensional segmentation of the cortical folds and global sulcal index. Automatically segmented cortical folds ((**a**), (**c**); in red) and smooth envelope of the brain mask ((**a**), (**b**); in blue) represented on two-dimensional magnetic resonance imaging slices ((**a**): coronal) and using mesh-based three-dimensional reconstruction ((**b**): brain hull surface—(**c**): cortical sulci and brain surface). (**d**): Reconstructed left hemispheres of subjects showing a high degree of overall sulcation (global sulcal index = 1.80) and a low degree of overall sulcation (global sulcal index = 1.46).

exposed surface,[29] which embodies additional information (included in the whole gyral contour length) related to the cortex thickness and the sulcal opening. In addition, the classical gyrification index captures the shape of the cortical folds, which are complex three-dimensional structures from measures on two-dimensional MRI slices,[29] whereas the g-SI is based on measures derived from a three-dimensional reconstruction of the sulcal surface.[13]

In a third step, a new automatic recognition algorithm based on a Bayesian framework to jointly identify and register sulci[30] (validated from 62 MRI with sulci manually labeled; mean recognition rate: 86%) was used to label the sulci in each hemisphere. Regional cortex folding was assessed by computing a regional sulcal index (r-SI), which was defined for twelve predefined regions (lateral face: dorsolateral prefrontal cortex, precentral sulcus, central sulcus, sylvian fissure, superior parietal cortex, inferior parietal cortex, temporal cortex, occipital cortex; medial face: medial frontal cortex, medial parieto-occipital cortex, basal temporal cortex; ventricle) as the ratio between the area of pooled labeled sulci (estimated from the sum of area of the mesh defining each sulcus) and the total outer cortex area in the corresponding hemisphere. Hence, the r-SI increases with the depth and the length of a sulcus. These twelve regions were defined a priori using the standard regional grouping of Brainvisa software (that is, 'sulcal_root_color' sulcus nomenclature).

For each subject, images at each processing step were visually checked. No segmentation error was detected. Of note, g-SI and r-SI were computed automatically, without any manual intervention.

Statistical analyses

Between-group differences in the global sulcal indices (g-SI) and brain volumes (hemispheric GM, WM and CSF volumes normalized to intracranial volume) were analyzed using mixed-design repeated measures ANOVA, with hemisphere ('Left' vs 'Right') as a within-subject factor and group ('A+VH' vs 'AH' vs 'HC') as a between-subject factor. When a significant main or interactive effect was detected, ANOVA was continued by post hoc analyses in each hemisphere separately using univariate linear models with patient group as factor. Complementary analyses were performed for the contrast 'AH vs A+VH', adding PANSS_P (PANSS positive subscale) as cofounding covariate to investigate the effects related to the sensory modalities of hallucinations while controlling from the global severity of positive symptoms. In addition, explorative regional post hoc comparisons between AH and A+VH were performed on the twelve predefined hemispheric r-SI.

Shapiro tests were used to check that the linear model residuals were normally distributed. Statistical significance was probed with F-tests in the ANOVA. A two-tailed P value < 0.05 was considered statistically significant. All the statistical analyses were carried out with R 2.12 software (Vienna, Austria; http://www.r-project.org/) with 'car' and 'effects' packages for the analysis of linear models.

RESULTS

Global analyses

The mixed-design repeated measures ANOVA revealed that the g-SI differed among the HC, patients with A+VH and patients with AH (that is, significant main effect of the group, $F = 108$; d.f. = 2; $P < 0.0005$), and this effect varied with hemisphere, as observed by the significant main effect of the hemisphere ($F = 15.8$; d.f. = 1; $P < 0.0005$). There was no interaction between the group and the hemisphere ($F = 1.1$; d.f. = 2; $P = 0.35$).

Post hoc analyses revealed significant bilateral differences between HC and schizophrenia subgroups with a greater g-SI in HC in the left and right hemispheres compared with patients with AH ($T > 10.9$, d.f. = 31, $P < 0.0005$) or A+VH ($T > 12.9$, d.f. = 31, $P < 0.0005$). Analyses of patients subgroups revealed a significant difference between AH and A+VH patients in the right hemisphere ($T = 2.26$, d.f. = 31; $P = 0.03$), with a g-SI decrease observed in patients with A+VH (1.55 ± 0.03) compared with patients with AH (1.64 ± 0.03) (Figure 2). In the left hemisphere, the g-SI decrease in patients with A+VH (1.53 ± 0.03) compared with patients with AH (1.59 ± 0.03) was not significant ($T = 1.55$; d.f. = 31; $P = 0.12$). Of note, the addition of normalized hemispheric GM or WM volumes, outer cortex area or cumulative treatment dose as covariates in the g-SI analyses yielded similar results. The differences between AH and A+VH patients in hemispheric g-SI were not accounted for by differences in the outer cortex surface area. Indeed, in the left hemisphere, the outer cortical area was 431.52 ± 8.36 cm^2 in

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patients with AH and 430.09 ± 8.61 cm^2 in patients with A+VH (T = 0.10; d.f. = 31; $P = 0.92$). In the right hemisphere, the corresponding areas were 430.55 ± 8.53 and 431.72 ± 8.79 cm^2 (T = 0.12; d.f. = 31; $P = 0.90$), respectively.

Complementary analyses in patient subgroups (AH vs A+VH), adding PANSS_P as a cofounding covariate to investigate the effects related to the sensory modalities of hallucinations while controlling for the global severity of positive symptoms, yielded similar main effects of group and hemisphere ($P < 0.0005$) but revealed a significant group-by-hemisphere interaction (F = 4.4; d.f. = 1; $P = 0.04$). Such a group-by-hemisphere interaction indicates a difference in the left–right asymmetry of g-SI (that is, the difference between the g-SI in the left and right hemispheres) between patients with A+VH (−0.016 ± 0.017) and patients with AH (−0.045 ± 0.013). The main effect of PANSS_P was not significant (F = 1.1; d.f. = 1; $P = 0.31$). Of note, the group-by-hemisphere interaction was no more significant (F = 1.8; d.f. = 1; $P = 0.19$) if PANSS_P was removed, in line with the analysis reported above involving AH, A+VH and HC.

These findings were specific for the cortex sulcation as mixed-design repeated measures ANOVA revealed no main or interactive effects of group or hemisphere on hemispheric GM, WM and CSF volumes normalized to intracranial volume (all $P > 0.05$).

Details of g-SI and brain volume data are reported in Table 2.

Explorative regional analyses in AH and A+VH

Regional post hoc analyses conducted on the patients subgroups revealed that the sulcation decrease in the A+VH group was not uniform: there was a decreased r-SI in the right parietal cortex (T = 2.27; d.f. = 31; $P = 0.03$) in A+VH patients (0.192 ± 0.006) compared with AH patients (0.213 ± 0.006) and in the left sylvian fissure (T = 2.33; d.f. = 31; $P = 0.03$) in A+VH patients (0.040 ± 0.004) compared with AH patients (0.054 ± 0.004). Similar results were obtained when PANSS-P was added as a covariate in the analyses.

These regional findings should be considered as exploratory because none held following Bonferroni correction for multiple testing (α-corrected = 0.002, that is, 0.05/26).

DISCUSSION

Despite their frequent occurrence in schizophrenia, the neural bases of VH have rarely been explored.[10] The current study provides the first structural evidence for neurodevelopmental deviations associated with VH in schizophrenia. Different cortical sulcation and left–right sulcal asymmetry were found between A+VH and AH patients, with a sulcation decrease in both A+VH and AH patients compared with HC. Such a comparison of subgroups of patients with or without VH allowed for the assessment of the specific effects of the hallucinatory modality and complement the more conventional comparison between schizophrenia patients and HC (the specific effects of VH must be distinguished from disease- or medication-related effects).

In this study, the early brain development was investigated from the analysis of the cortical morphology.[12] Indeed, the mature sulco-gyral pattern is considered to result from early processes that shape the cortex anatomy from a smooth lissencephalic structure to a highly convoluted surface. This complex folded surface has been shown to be an early marker of later functional development.[31] Several factors contribute to the neurodevelopmental processes that influence the shape of the folded cerebral cortex,[12] including the structural connectivity through axonal tension forces.[32,33] These mechanical constraints lead to a compact layout that optimizes the transmission of neuronal signals between brain regions[34] and thus brain network functioning. Furthermore, experimental lesion studies in monkeys have indicated that the disruption of afferent pathways, when it occurs early in pregnancy, that is, before the formation of cortical pathways linking the visual areas, can lead to the emergence of abnormal sulcation in the occipital lobe.[35,36] A similar early difference in WM connectivity might explain the difference in sulcation detected between AH and A+VH patients. This interpretation is supported by recent brain imaging studies reporting abnormal anatomo-functional connectivity in schizophrenia patients with VH.[10,37,38] In addition, the difference in sulcation asymmetry detected between A+VH and AH patients may reflect difference of functional specialization. The association between hemispheric functional specialization and the asymmetry of the cortex sulcation is supported by studies of the corpus callosum, a large bundle of inter-hemispheric fibers, showing that asymmetrical brains have fewer and/or thinner fibers connecting the two hemispheres relative to more symmetrical brain, as evidenced by a reduced midsagittal area[39] and microstructural integrity measured using diffusion MRI.[40] Furthermore, it is more efficient to transfer information between close areas within the

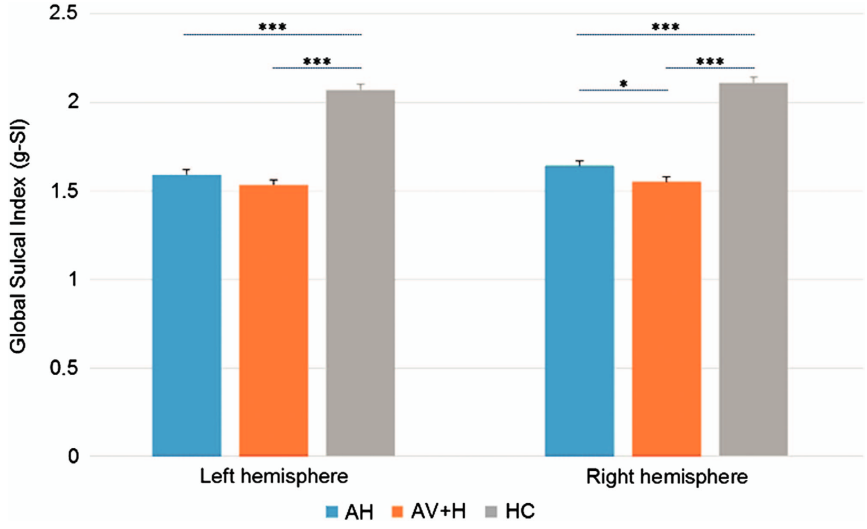

Figure 2. Global sulcal index in healthy controls ($n = 17$), patients with auditory hallucinations only ($N = 17$) and patients with audio–visual ($N = 16$) hallucinations. Average global sulcal index in the left and right hemispheres in healthy controls (in gray), schizophrenia patients with auditory hallucinations (in blue) or audio–visual hallucinations (in red). Error bars denote the standard deviation.

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Table 2. Global sulcal index and global volumes in healthy controls ($n = 17$), patients with auditory only ($N = 17$) and patients with audio–visual ($N = 16$) hallucinations

	HC	*AH*	*A+VH*
Left hemisphere			
Global sulcal index	2.07 (0.03)	1.59 (0.03)	1.53 (0.03)
Normalized GM volume, %	46.65 (0.88)	45.66 (0.92)	45.20 (0.91)
Normalized WM volume, %	38.83 (0.59)	38.62 (0.59)	39.52 (0.60)
Normalized CSF volume, %	14.51 (0.72)	15.70 (0.72)	15.27 (0.74)
Right hemisphere			
Global sulcal Index	2.11 (0.03)	1.64 (0.03)	1.55 (0.03)
Normalized GM volume, %	46.78 (0.85)	45.90 (0.85)	45.51 (0.88)
Normalized WM volume, %	38.72 (0.60)	38.61 (0.60)	39.19 (0.62)
Normalized CSF volume, %	14.50 (0.70)	15.48 (0.70)	15.29 (0.72)

Abbreviations: AH, auditory hallucinations; A+VH, audio–visual hallucinations; CSF, cerebro-spinal fluid; GM, gray matter; HC, healthy controls; WM, white matter. Data are presented as means (s.e.m.).

same hemisphere rather than between distant areas distributed in the two hemispheres.[41,42] Such an interpretation is in line with Crow's previous work proposing that decreased brain asymmetry, associated with abnormal hemispheric functional specialization, is a core pathophysiological mechanism of schizophrenia.[43,44]

Because structural brain asymmetries are determined during fetal life,[42,45,46] in the same developmental window as sulcation processes, our findings provide converging evidence of a neurodevelopmental origin for VH in schizophrenia, in line with clinical studies showing that VH are associated with early disturbances in the brain development.[16–18] We speculate that reduced right but not left hemispheric sulcation might result in VH because of the functional organization of the visual system and, more specifically, its right hemisphere dominance for high-level processing.[47] A recent study of intracerebral electrical stimulation in epileptic patients[48] supports this hypothesis. Indeed, complex VH (that is, meaningful visual hallucinations including face, landscape, animal and body parts) that are typically reported in schizophrenia[3] were shown to be exclusively evoked by stimulating the right hemisphere, whereas elementary VH, that is, a spot or a blob, were similarly evoked by stimulating either the right or left hemisphere.

Considering VH as a marker of deviations during the early neurodevelopmental processes allows reinterpretation of clinical aspects of hallucinations. Hence, the greater clinical impairment and greater compromise of overall functioning reported by patients experiencing VH[18] may relate to the greater neurodevelopmental weight in this subgroup of patients.[18] Similar associations between specific clinical features and early brain development have been reported in recent schizophrenia studies. Different sulcation was notably found between patients with different phenomenological properties, such as inner space AH or outer space AH.[15] Outside the hallucinatory dimension, the presence of neurological soft signs—that is, observable defects in motor coordination, motor integration and sensory integration[49] related to pre- and perinatal impairments[50–52]—have also been found associated with decreased sulcation.[25]

Explorative regional analyses revealed difference in the right superior parietal cortex and in the left Sylvian Fissure in A+VH patients. Sulcal differences in the right superior parietal cortex may be associated with functional impairments in the dorsal attentional network and the default-mode network (DMN) that overlap this cortical area. The study of spontaneous fluctuations at rest previously revealed a disrupted intrinsic connectivity during the occurrence of auditory hallucinations[53–56] and more recently during audio–visual hallucinations.[57] This last study, conducted in first-episode psychosis, reported a dynamic interaction between association sensory cortices and the DMN during A+VH. Sensory and DMN networks were found to be anticorrelated during the experience of hallucinations. Furthermore the DMN spatial and temporal instability persisted during non-hallucinatory periods.[57] Interestingly, impaired interactions with the DMN have also been suggested in the pathophysiology of VH in Parkinson Disease (PD),[58] but in contrast to first-episode psychosis in which the DMN seems primarily and intrinsically affected, an external interference with DMN through aberrant interactions with attentional networks have been proposed in PD.[58]

The precise role of the Sylvian fissure in VH is not straightforward and will require further investigation. It is however interesting to note that our recent multimodal brain imaging study in patients with VH detected an increase in the fractional anisotropy, a diffusion MRI marker of local WM microstructure, within the left superior longitudinal fasciculus that runs above the Sylvian fissure in A+VH patients when compared with AH patients.[10]

The results of this study are best understood in the context of a number of methodological issues. Cortical folds are complex and variable three-dimensional structures,[59] and their shape is difficult to reliably describe based on two-dimensional MRI slices.[28] The use of three-dimensional mesh-based sulcal indexes[13] has provided an accurate assessment of the cortex morphology as in our previous studies in schizophrenia.[13,15,24,25] This study focused on sulcation because cortical sulci can be reliably defined using simple geometric properties,[28] whereas the gyri are relatively difficult to reliably define from a purely geometrical point of view, especially for the borders not limited by sulci.[60] The moderate sample size used in this experiment should be acknowledged. However, the high group homogeneity allowed us to address strong a priori hypotheses and draw significant conclusions.

In conclusion, although the literature already has provided evidence for specific association between VH and neurodegenerative mechanisms (for example, with Body-Lewy Dementia or Parkinson Disease),[3] this study provides the first evidence of an association between VH and neurodevelopmental mechanisms in schizophrenia. Future studies are needed to further test this theory, for instance from the longitudinal analysis of brain trajectory[61] in VH patients, coupled with pathway analyses[62] of genes involved in neurodevelopment and neuroplasticity.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

All the authors designed the study; AA, PT, JB, RJ recruited the participants; JB & RJ acquired the MRI data; AC, AA, RJ performed the analyses; All the authors contributed to the manuscript writing.

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III.La plasticité activité-dépendante

Dans cette partie, nous allons nous intéresser à un modèle de plasticité chez des sujets sans pathologie qui pourra être utilisé, dans un second temps, à visée thérapeutique chez des jeunes patients souffrant de troubles du spectre autistique. En effet, la NP sous-tend non seulement le développement et la maturation normaux, mais aussi l'apprentissage des compétences et la mémoire, ainsi que les conséquences de la privation sensorielle ou de l'enrichissement environnemental (Kolb et Muhammad 2014). Des études animales ont ainsi identifié, chez l'adulte, une augmentation de la neurogenèse, de la synaptogénèse, de l'angiogenèse et de la libération de neurotrophines à la suite d'un apprentissage et/ou de l'exercice physique (Hötting et Röder 2013). Au cours de ces dernières années, l'apprentissage de la musique a suscité un intérêt croissant en tant que paradigme pour l'étude de la NP exercice-dépendante (Herholz et Zatorre 2012).

Dans l'étude présentée ci-dessous, nous avons comparé la connectivité fonctionnelle de repos (rs-FC) chez des jeunes adultes : 15 participants novices sains avant et après un cours de batterie (séances de 30 minutes de batterie, 3 jours par semaine pendant 8 semaines) et chez 16 participants novices appariés sur l'âge. Afin d'identifier les régions du cerveau présentant des différences significatives de connectivité fonctionnelle avant et après l'apprentissage de la batterie, sans régions d'intérêt a priori, une analyse multivariée a été effectuée (MVPA : *Multivariate Pattern Analysis*). Nous avons ainsi pu mettre en évidence que l'apprentissage de la batterie était associé à une augmentation de la connectivité fonctionnelle au niveau de la partie postérieure des gyri temporaux supérieurs bilatéraux (pSTG). Ces régions ont ensuite été utilisées pour effectuer une analyse de connectivité fonctionnelle par région d'intérêt. Le pSTG présentait une augmentation de connectivité fonctionnelle au niveau des aires prémotrices et motrices, du lobe pariétal droit et une diminution de connectivité fonctionnelle au niveau du cervelet.

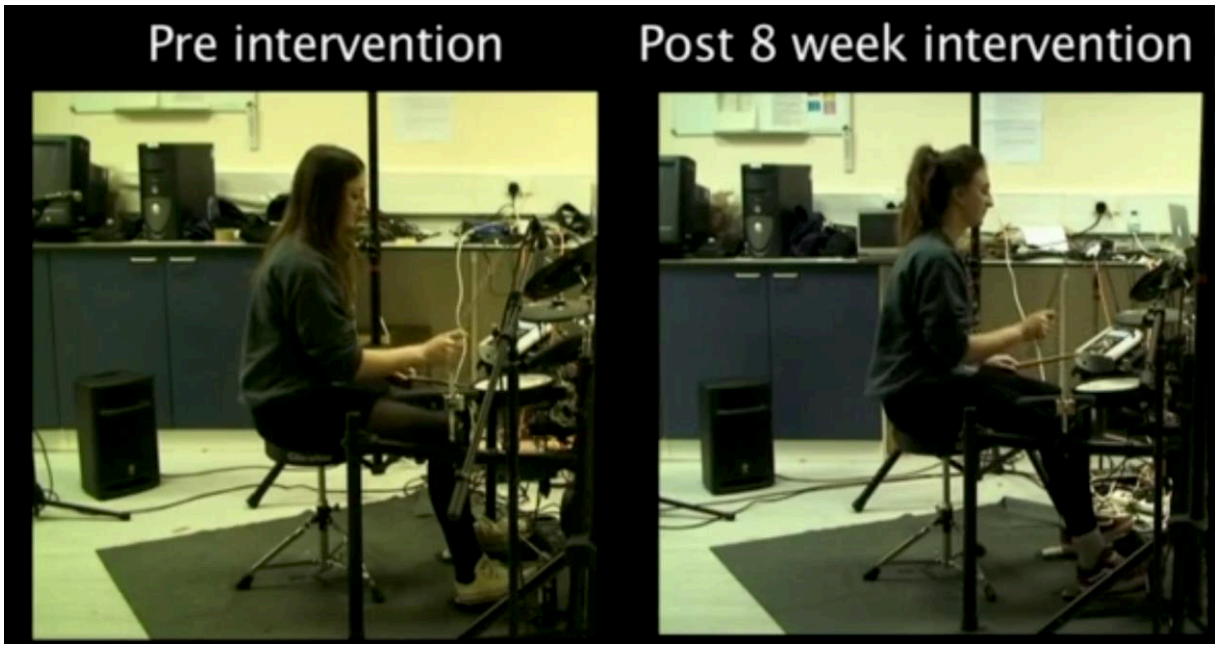

Figure 4 Image d'une participante avant et après avoir appris à jouer de la batterie. La vidéo complète peut être visualisée ici : https://vimeo.com/141911618.

De façon intéressante, la plupart des régions mises en évidence par les analyses en région d'intérêt (lobule pariétal inférieur, lobule pariétal supérieur, gyrus temporal moyen, gyrus temporal supérieur) font partie du système de neurones miroirs humains (SNM), qui est activé lorsqu'un individu effectue une action et lorsqu'une action similaire ou identique est observée passivement. Il est également supposé que le SNM soutient les processus émotionnels et les bénéfices sociaux associés à la musique. En effet, la musique a été décrite comme un trait humain universel, offrant un mode de communication unique qui peut unir et définir des groupes sociaux, des générations et des cultures (Molnar-Szakacs et Overy 2006).

D'un point de vue clinique, nos résultats pourraient être particulièrement intéressants pour envisager une intervention centrée sur l'apprentissage de la batterie dans les troubles impliquant un dysfonctionnement des SNM tels que les troubles du spectre autistique (TSA). Il est intéressant de noter que les personnes atteintes de TSA éprouvent des difficultés de communication et de compréhension des émotions dans le domaine social, comme la capacité d'interpréter les expressions non verbales, faciales et corporelles d'autres personnes. Et il a été suggéré que l'apprentissage de la batterie avec un partenaire social pourrait être particulièrement pertinent pour ces patients, certains

résultats ayant même montré une amélioration des habiletés motrices et psychosociales chez des enfants souffrant de TSA (Lowry et al. 2019). Une étude impliquant des patients TSA qui apprennent à jouer de la batterie et qui ont bénéficié d'une IRM avant et après cet apprentissage est actuellement en cours de finalisation en collaboration avec le Centre for Neuroimaging Science à l'Institute of Psychiatry de Londres.

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ORIGINAL ARTICLE

Motor Learning Induces Plasticity in the Resting Brain—Drumming Up a Connection

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Abstract

Neuroimaging methods have recently been used to investigate plasticity-induced changes in brain structure. However, little is known about the dynamic interactions between different brain regions after extensive coordinated motor learning such as drumming. In this article, we have compared the resting-state functional connectivity (rs-FC) in 15 novice healthy participants before and after a course of drumming (30-min drumming sessions, 3 days a week for 8 weeks) and 16 age-matched novice comparison participants. To identify brain regions showing significant FC differences before and after drumming, without a priori regions of interest, a multivariate pattern analysis was performed. Drum training was associated with an increased FC between the posterior part of bilateral superior temporal gyri (pSTG) and the rest of the brain (i.e., all other voxels). These regions were then used to perform seed-to-voxel analysis. The pSTG presented an increased FC with the premotor and motor regions, the right parietal lobe and a decreased FC with the cerebellum. Perspectives and the potential for rehabilitation treatments with exercise-based intervention to overcome impairments due to brain diseases are also discussed.

Key words: fMRI, learning, music, neuroplasticity, resting-state

Introduction

Neuroplasticity (NP) is defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function, and connections. Neuroplasticity underlies not only normal development and maturation but also skill learning and memory, as well as the consequences of sensory deprivation or environmental enrichment (Kolb and Muhammad 2014). Even if NP was initially thought to be limited to critical periods in development, it is now largely accepted to occur throughout the lifespan. In fact, animal studies have identified an enhancement of adult neurogenesis, synaptogenesis, angiogenesis, and the release of neurotrophins as a consequence of learning and/or physical exercise (Hötting and Röder 2013). Moreover, several famous neuroimaging investigations demonstrate adaptative neuroplastic modifications in the structure (Maguire et al. 2000; Draganski et al. 2004; Driemeyer et al. 2008) and function (Lewis et al. 2009) of the human brain in response to environmental demands in healthy adults (Wan and Schlaug 2010). Interestingly, few of these neuroimaging studies have investigated neuroplastic modifications following physical activity.

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These existing studies have mainly focused on cognitive facilitation by cardiovascular exercise in older adults, failing to investigate young participants or different types of physical activity (Voelcker-Rehage and Niemann 2013).

Over the past decades, musical training has gained increasing interest as a paradigm to study human experience-related NP in the same general model framework (Herholz and Zatorre 2012). Playing a musical instrument is a highly complex task and requires multimodal skills such as bimanual motor activity dependent on multi-sensory feedback, fine motor skills coupled with metric precision, musical memorization (Wan and Schlaug 2010), and improvization (Pinho et al. 2014; Beaty 2015). These skills involve complex interactions, between sensory and motor systems and high-order cognitive processes, which have to be coordinated at a high degree of synchrony and accuracy (Zatorre et al. 2007).

There is increasing evidence from several different neuroimaging modalities that NP is associated with musical training. By using structural neuroimaging, Gaser and Schlaug reported gray matter volume differences in motor, auditory, and visual–spatial brain regions when comparing professional musicians (keyboard players) with matched groups of amateur musicians and nonmusicians (Gaser and Schlaug 2003). Cerebral activity patterns associated with musical perception in musicians have also been studied by using functional MRI (fMRI). A significant difference in the degree of activation between musicians and nonmusicians was noted in the temporal regions and for musicians the degree of activation was correlated with the age at which the person had begun musical training (Ohnishi et al. 2001). Functional MRI was also used to explore the brain activations of novices trained to play sequences on a piano keyboard (Lahav et al. 2007; Chen et al. 2012; Herholz et al. 2015) or to listen and imitate different auditory rhythms (Chen et al. 2007). These studies showed complex interactions between auditory and motor brain regions that were associated with musical training.

Interestingly, drumming, which is a coordinative exercise combining musicality, body coordination, cardiovascular exercise, "bilateral" arm, leg movements, and sensorimotor integration processes (De La Rue et al. 2013), has not been studied extensively to date. Only expert drummers have been studied thus far. While Tsai et al. (2012) have shown that the posterior temporal lobes are essential for audio-motor processing, Petrini et al. (2011) showed that expert drummers present a reduced activation bilaterally during an audiovisual task in the cerebellum and the left parahippocampal gyrus, respectively, involved in action–sound representation and audiovisual integration.

Recently, resting-state functional connectivity (rs-FC) analyses have been widely used to investigate neuroplastic modifications. Rs-FC corresponds to the temporally correlated, low-frequency spontaneous fluctuations of blood oxygen level-dependent signals across brain regions that occur when a participant is not performing an explicit task (Fox and Raichle 2007). Temporal correlations do not appear to be random, as patterns of connectivity have been reliably identified across studies and participant. Moreover, it is now widely accepted that the strength of correlations within and between networks has behavioral relevance (Guerra-Carrillo et al. 2014). Interestingly, it has been proposed that rs-fMRI is an effective measure of plasticity and that rest activity patterns reflect the history of repeated synchronized activation between brain regions. Thus, the study of rs-FC is particularly adapted to highlight neuroplastic modifications (Buckner and Vincent 2007; Guerra-Carrillo et al. 2014).

In this article, we have compared the rs-FC in 15 novice healthy participants, by using a fully data-driven approach, before and after a course of drumming with another 16 novice participants who were again evaluated longitudinally but with no intervention. This longitudinal design was used to disentangle cause and effect by investigating the same participants before and after the course of drumming. We hypothesized that participants would exhibit a higher level of functional connectivity (FC) in the sensory and motor systems after drum training during the resting state, which could not be attributed to the MRI session effects (anxiety, novelty of the MRI environment).

Material and Methods

Participants

Thirty-one young healthy volunteers (16–19 years) with no prior drumming experience and with no psychiatric or neurological disorders participated in the study after providing written informed consent. In The King's College, London, College Research Ethics Committee approved the experimental protocol. Participants were randomly divided into 2 groups: drum group and control group.

Procedure

Assessment

All participants were attended in to the Institute of Psychiatry Psychology and Neuroscience (IoPPN) at King's College London for 2 scanning sessions. At the first scanning session (t1), the Edinburgh Handedness Inventory Short Form (EHI) for daily activities (e.g., writing, throwing. . .) (Veale 2014) was used to assess each participant's hand dominance. Responses were coded to generate a Laterality Quotient (scores ranging from −100 to 100), which was then used to classify individuals into left handers (−100 to −61), mixed handers (−60 to 60), and right handers (61 to 100). Moreover, to assess the baseline drumming ability and musical experience, a self-report measure was created. Participants reported their level of skill and length of involvement in drumming, playing of another musical instrument and involvement in dance or singing. Responses for all domains were coded on an ordinal scale (0, no experience; 1, some experience, no formal instruction; 2, limited formal instruction but not recent; 3, formal instruction, less than 4 years but not current; 4, formal instruction, exams achieved, greater than 5 years involvement and current).

Drumming

Following the first drumming assessment and scanning session the drum group took part in three 30-minute low intensity group drumming sessions per week for 8 weeks. Each session was delivered by a professional drum tutor and comprised 4 integrated parts: (1) a warm up, focused on beating the drum with a relaxed and consistent motion of the drum sticks; (2) snare drum "rudimental" exercises, played on a single drum surface, adopting a "flow sticking" approach to sequences of left and right hands (Queen 2007); (3) coordinated "groove" patterns, incorporating the interplay of bass drum (right foot) and the hi-hat pedal (left foot) with rock/pop back beat ostinato patterns played on the hi-hat or ride cymbal and snare drum, including eighth note (quaver), quarter note (crotchet), sixteenth note (semiquaver), syncopated quarter note and shuffle ostinato patterns (Chaffee 1980); and (4) performance of learned "grooves" and "fill-ins" to accompany well-known popular music songs. The complexity of drumming tuition was increased on a weekly basis in line with participants' demonstration of improved drumming coordination and technique. The control participants

were asked to not take part in any musical activities. After the 8 weeks, (t2) participants came back to the IoPPN for a second drumming assessment and scanning session.

All of the drumming was performed on electronic drum sets for both drumming training (HD3, Roland, Nakagawa, Japan) and assessment (TD9, Roland, Nakagawa Japan) with a standard right-handed 5 piece configuration comprising a snare drum, 3 tom-toms, hi-hat, ride cymbal, crash cymbal, bass drum, and hi-hat pedal (played with the feet). Drumming was assessed following a short coaching period on the participants' ability to play a simple 4 quarter note pattern to the song "Green Onions" (Booker T and the MGs, Stax/Atlantic, 1962) and a simple 8 eighth note pattern, consisting of regular eighth note hi-hats with alternating kick and snare on the main beats of the bar, to the song "Billy Jean" (Michael Jackson, EPIC, 1982). Versions without tempo fluctuations were used, created using the software "Live" (V9.1, Ableton, Berlin). This software analyzed the beat points of the original recording and adapted them temporally to ensure that the version of the song heard by the participants was at a constant tempo, with a consistent and precise inter beat interval so errors could be accurately recorded. The songs were played out of a single speaker on one channel, while the underlying beat locations were indicated by recording a click track on a second channel. A standard onset detection algorithm (Bello et al. 2005) was used to determine the audio buffer frame in which the transient of each beat in the click track occurred. A precise onset detection method was then used to find the onset location by iteratively dividing the audio buffer into window segments and determining the window in which the energy change was maximal at successively smaller window sizes. Thereby, a precise sample was specified for each beat location, accurately placed on the transient of each audible click (Robertson 2014). Timing data were exported from the drum set using the musical digital interface (MIDI) signal. A comparison with a piezo microphone placed on the snare indicated that the recorded MIDI events were a maximum of 4 ms from the detected onset using audio-based methods, and generally much closer. Drumming ability was assessed objectively as the percentage of bars of both patterns that were completed during two 2-min periods of data capture (1–3 min of each song). To record a completed bar all elements had to be present in each pattern and within half a beat (250 ms for 4 quarter note pattern and 125 ms for an 8 eighth note pattern) of the perfect timing. We also evaluated the error in events that should have been synchronous (flamming) as flam error per bar in milliseconds. For each note of the bar, we evaluated the time between the 2 events. When 3 limbs were involved, we evaluated the difference between the first and last event. This was only evaluated for completed bars, as it would be impossible to make a meaningful measurement where the pattern was breaking down or parts were missing. No practice of either song used in the assessment was included in the 8 weeks drumming training. While a drum flam can be a sought-after stylistic feature of a pattern, flams were not part of the stylistically correct performance for the 2 chosen patterns.

MRI Acquisition and Preprocessing

All participants were scanned in a 3T MR scanner (Discovery MR750, General Electric, Milwaukee, WI, USA). All participants underwent an anatomical T_1-weighted MRI using a gradient-echo sequence with the following scan parameters: 196 sagittal slices, time repetition (TR) = 7.3 ms, time echo (TE) = 3 ms, time to inversion (TI) = 400 ms, FA = 11°, field of view (FOV) = 270 mm², matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm^3, slice thickness = 1.2 mm. The rs-functional magnetic resonance imaging (fMRI) was collected using an echo-planar imaging sequence with the following scan parameters: 180 volumes, interleaved ascending slice order, TR = 2000ms, TE = 30 ms, FA = 75°, FOV = 211 mm², matrix size = 64 × 64, voxel size = 3 × 3 × 3 mm^3, gap = 0.3 mm. Four dummy scans were obtained before each fMRI data acquisition to allow for the equilibration of the MRI signal. During acquisition, the participants remained with eyes open attending a cross-hair on the screen in a wakeful resting state. Headphones and earplugs were used to attenuate the acoustic noise of the scanner.

The anatomical and functional data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12) and the CONN toolbox Version 14p (http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon 2012). Functional data were preprocessed using a slice scan time correction, realignment (motion correction), registration to structural images and spatial normalization to Montreal Neurological Institute (MNI) standardized space, smoothing with a Gaussian filter of 5.0 mm spatial full width at half maximum value. A conventional band-pass filter over a low-frequency window of interest (0.008–0.09) was also applied to the resting-state time series. After these preprocessing steps, a CompCor strategy (Behzadi et al. 2007) was implemented, extracting signal to noise from the white matter (WM) and cerebrospinal fluid (CSF) by principal component analysis without affecting intrinsic FC (Chai et al. 2012). These components (WM and CSF) and motion parameters were included in the model and considered as covariates of no-interest.

Voxel-to-voxel Analysis

To identify brain regions showing significant FC differences before and after drumming without having to restrict the analyses to one or several a priori regions of interest (ROI), whole-brain connectivity analysis was performed. In the present study, we employed the "connectome-MVPA" approach (multivariate pattern analysis of whole-brain connectome) implemented in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). In this approach, a low-dimensional multivariate representation characterizing the connectivity pattern between one voxel and the rest of the brain was created for each voxel separately. This representation was defined by performing a principal component analysis characterizing the FC between this voxel and the rest of the brain. The resulting component scores were then stored as functional maps and entered into standard second-level analyses for between-condition tests (i.e., before and after drum training). Finally, an *F*-test was performed, comparing (for each voxel) the component scores across the 2 conditions. Therefore, the second-level statistical analysis provided a multivariate pattern of correlated voxel clusters associated with drumming. In other words, regions that are significant in the resulting voxel-level analyses indicate condition-related differences in connectivity between those areas and the rest of the brain. More technical details and an example of the use of the connectome-MVPA method can be found in Whitfield-Gabrieli et al. (2015) and in Beaty et al. (2015).

Seed-to-voxel Analyses

To explore which specific aspects of the FC between clusters found in the voxel-to-voxel analysis and the rest of the brain was different between the conditions, a post hoc seed-to-voxel analysis was performed. Therefore, 10 mm spherical ROI based on peak activation clusters from the whole-brain connectivity analysis were extracted and used as seeds to perform seed-to-voxel analysis. Correlations maps were then calculated for each

participant, per condition, by extracting the mean signal time course from the seeds and computing Pearson's correlations coefficients with the time course of all other voxels of the brain. Those correlation coefficients were converted to normally distributed z-scores using the Fisher transformation to allow for second-level general linear model analyses. Second-level within group (one sample *t*-tests) and between group (ANOVA) analyses were performed on the average Z-maps from the new seeds source ROIs. Finally, a paired *t*-test was performed to examine the change of resting-state connectivity before versus after drum training for all participants.

For confirmatory analysis, seed-to-voxel analyses were applied using anatomically defined ROIs, in order to avoid potential concerns regarding circularity. For this analysis, the posterior superior temporal gyrus (pSTG) was chosen because it is a crucial hub engaged in sensorimotor integration (Rauschecker and Tian 2000; Scott et al. 2009), auditory–motor transformations (Warren et al. 2005; Chen et al. 2007) and because it is selectively responsible for action-related sounds (Zatorre et al. 2007; Tsai et al. 2012). Moreover, a recent fMRI meta-analysis of 43 studies on experimental auditory–motor training (i.e., finger tapping), revealed activity in the pSTG (Chauvigné et al. 2014). Two 10 mm spherical ROIs were then created based on the Harvard-Oxford cortical atlas implemented in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). The MNI coordinates of left and right pSTG were, respectively, (−62, −29, 3) and (61, −24,1).

As gender and handedness may be a factor which modulates musical training (Koelsch et al. 2003; Klöppel et al. 2007) additional analyses including gender and handedness as covariates were conducted. The same 10 mm spherical ROIs were used as seeds in the control group in order to delineate brain changes which are specific to the drum training. To precisely identify the brain areas involved, the Harvard-Oxford Cortical and Subcortical Atlas (Desikan et al. 2006; Makris et al. 2006), the AAL Atlas (Tzourio-Mazoyer et al. 2002), and the Juelich Histological Atlas (Eickhoff et al. 2007) were used. All results were thresholded at a voxel-wise $P < 0.001$ and at the cluster extent $P < 0.01$ FWE corrected. For confirmatory analysis, results were thresholded at a voxel-wise $P < 0.001$ and at the cluster extent $P < 0.05$ FWE corrected, a threshold widely used in confirmatory analysis (Kriegeskorte et al. 2010; Chen et al. 2015).

Correlations with Drum Progression

To evaluate the association between FC and drum progression, correlations (Pearson's coefficients) were performed between the drum progression scores in each participant and the connectivity values (z-scores) of regions showing significant differences after drum training from the seed-to-voxel analysis. Two scores were used. The first score corresponded to the mean number of bars successfully completed (Δ% bars completed) before versus after the drum training (t2 – t1 difference) from "Green onions" and "Billy Jean". The "combined progression score" corresponded to the proportion of bars successfully completed before versus after the drum training (t2 – t1 difference) as the percentage of bars completed (Δ% bars completed) from both songs.

Statistical Analyses

Statistical analyses of demographic data and drum performance were performed using SPSS (SPSS version 18, Chicago, Illinois, USA). Independent sample *t*-tests or Mann–Whitney rank sum test, and paired *t*-tests were used to determine baseline differences, and the effects of drum training between and within groups. To test whether there was a significant interaction of group over time, we performed a repeated-measures ANOVA model by specifying "time" as a within-subjects contrast (t1 – t2, i.e. before and after the drum training) followed by a between subject's contrast (drummers vs. controls). Significance was set at $P < 0.05$.

Results

Participants and Drum Progression

Based on a self-report measure, the drum group ($n = 15$, 7 men, 8 women, 2 mixed-handed, age 16.8 ± 0.7 years) and the control group ($n = 16$, 8 men, 8 women, all right-handed, age 17.8 ± 1.4 years) presented no prior drumming experience (all scores ≤2). Moreover, there were no statistical differences between the 2 groups in terms of self-reported other musical instrument ($P = 0.53$) dance and singing experience ($P = 0.31$).

At baseline, the mean number of bars successfully completed for "Green Onions" and "Billie Jean" was not significantly different between the 2 groups (respectively, $P = 0.42$ and $P = 0.12$) (see Fig. 1). After 8 weeks, the mean number of bars successfully completed was significantly increased in both groups and for the 2 songs (see Fig. 1). The mean combined progression score was significantly higher ($P = 0.003$) for the drum group (mean = 0.45 ± 0.29) in comparison with the control group (mean = 0.17 ± 0.19). A before/after video is available for illustration (see https://vimeo.com/141911618).

For "Green Onions", repeated-measures ANOVA revealed no significant effect of group ($F = 3.9$, $P = 0.07$), a significant effect of time ($F = 19.9$, $P = 0.001$) and no group × time interaction ($F = 3.3$, $P = 0.091$). For "Billie Jean", repeated-measures ANOVA revealed a significant effect of group ($F = 26.1$, $P < 0.001$), a significant effect of time ($F = 36.1$, $P < 0.001$) and significant group × time interaction ($F = 21.9$, $P < 0.001$). There was no significant difference in flam error per bar between t1 and t2 in both groups ($P = 0.24$).

Voxel-to-voxel Analysis

The connectome-MVPA analysis revealed 2 symmetric clusters associated with drum training ($P < 0.005$, FWE correction). These clusters consisted of the posterior division of the left and right superior temporal gyri (STG) and middle temporal gyri (MTG) and are described as pSTG throughout the manuscript (see Table 1 and Fig. 2).

Seed-to-voxel Analyses

Group-level seed-to-voxel analyses revealed increased FC after drum training when compared with before between left pSTG and left superior parietal lobule (SPL), left inferior temporal gyrus, right angular gyrus, right supramarginal gyrus, left and right lateral occipital cortex, right inferior temporal gyrus, and left inferior frontal gyrus and a decreased FC between the right STG and MTG (posterior division) and left and right cerebellum crus I and II (see Fig. 3). Peak spatial coordinates in the MNI space and the corrected *P*-value ($P < 0.01$, FWE correction) are reported in Table 2.

Group-level seed-to-voxel analyses revealed increased FC after drumming when compared with before between right pSTG and right supramarginal gyrus right angular gyrus, right SPL and right pre- and postcentral gyrus and a decreased FC with the left STG and MTG (posterior division), left temporal pole, bilateral cerebellum crus I and II, left paracingulate gyrus and right MTG (see Fig. 4). Peak coordinates in the MNI space

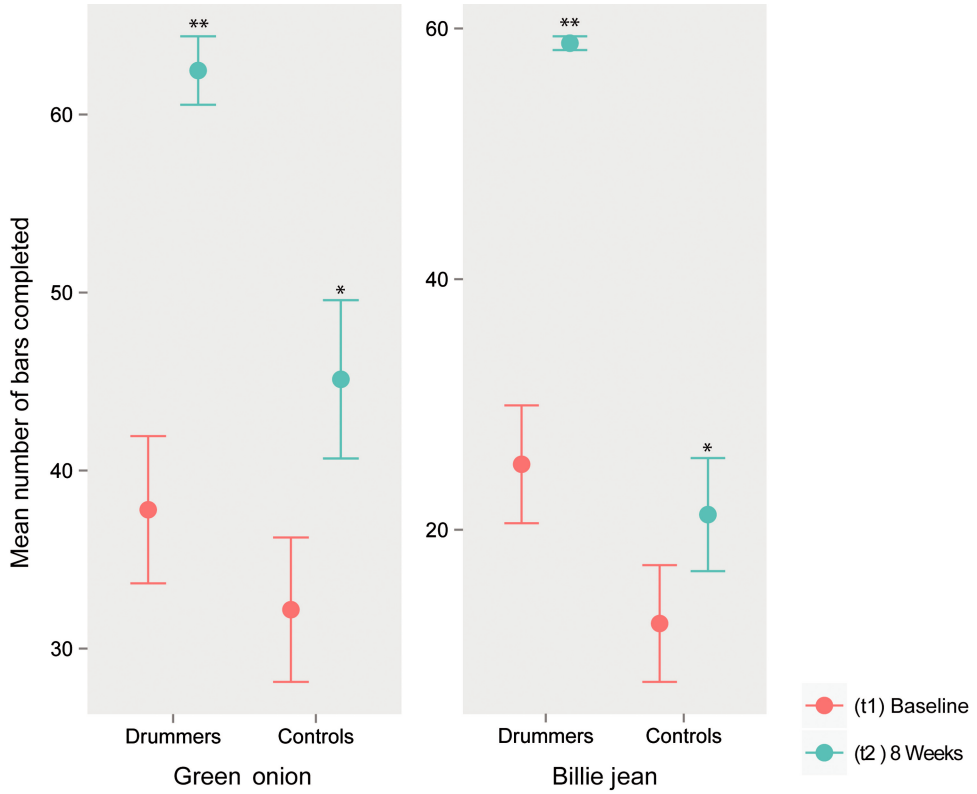

Figure 1. Mean number of bars successfully completed for "Green Onions" and "Billie Jean" before and after the drum training. At baseline, the mean number of bars successfully completed was not significantly different between the two groups for the both songs (respectively $P = 0.42$ and $P = 0.12$). After 8 weeks, the mean number of bars successfully completed was significantly increased in both groups and for the 2 songs. Error bars denote the standard deviation. *$P < 0.05$; **$P < 0.001$.

Table 1 Whole-brain connectome-MVPA analysis (voxel-to-voxel analysis)

Cluster size	Side (L/R)	Brain areas	MNI coordinates			F_{max}	Z_{max}	P_{corr} value
			x	y	z			
160	L	Superior Temporal Gyrus (posterior division)	−64	−28	12	15.02	4.78	<0.001
		Middle Temporal Gyrus (posterior division)	−58	−26	−8	9.00	3.72	
49	R	Superior Temporal Gyrus (posterior division)	64	−18	02	11.71	4.25	<0.005
		Middle Temporal Gyrus (posterior division)	70	−28	0	8.80	3.67	

Note: MNI coordinates (x, y, z) represent peaks within a cluster. Cluster size corresponds to spatial extent (i.e., number of voxels). Correction for multiple comparisons was performed using family-wise error correction at the cluster level.
L/R, left/right side of the brain.

and the corrected P-value ($P < 0.01$, FWE correction) are reported in Table 3.

The seed-to-voxel analysis was confirmed by adopting new, anatomically defined ROIs, as we observed qualitatively the same patterns of modulated FC involving the same networks (see Supplementary Tables 1 and 2).

The supplementary inclusion of gender and handedness as covariates did not change the results as the same clusters were found. No significant FC differences were observed in the control group.

Improvement in Performance and Correlations with Functional Connectivity

Participants with higher improvement in performance had higher right seed-right parietal lobe connectivity scores. Indeed, there was a significant correlation between the improvement in the mean number of bars successfully completed for "Billie Jean", the combined progression score and the right parietal lobe FC (including the right supramarginal gyrus, the right angular gyrus and the right SPL) from the right seed. The correlation coefficients were, $r = 0.60$ ($P = 0.02$) and $r = 0.57$ ($P = 0.03$), respectively (see Supplementary Figure). The improvement in performance did not correlate significantly with the FC of the other clusters.

Discussion

The main goal of this study was to determine whether we could visualize significant differences in the functional networks engaged in drum training in healthy participants by using rs-FC. Drum training was characterized behaviorally in significantly

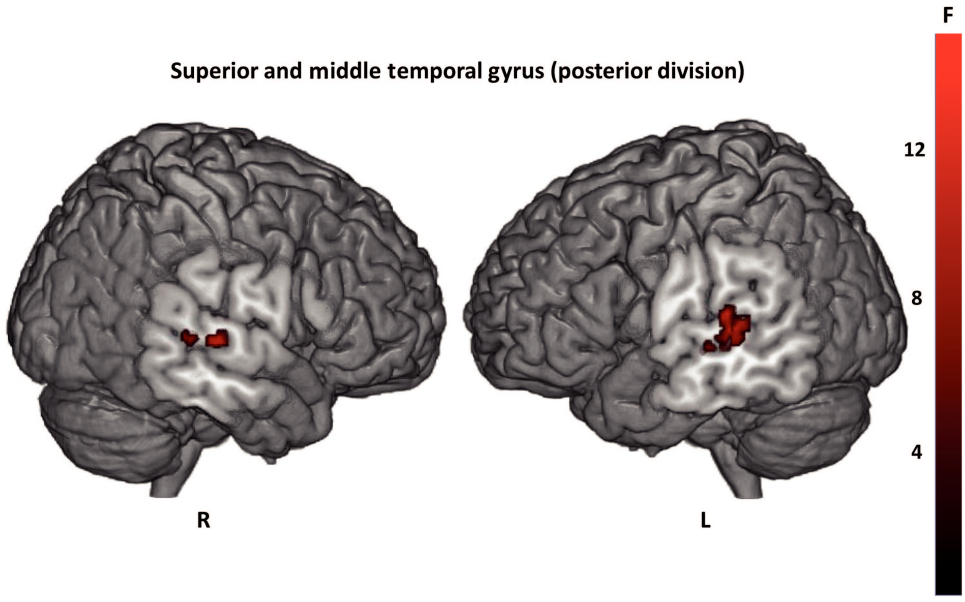

Figure 2. Results from the voxel-to-voxel analysis showing areas of highest connectivity in the whole brain by comparing before versus after drum training. These clusters consisted of the posterior division of the left and right STG and MTG and are described as pSTG. This map is based on F-contrasts thresholded at $P < 0.01$, FWE corrected. Clusters were rendered on the "ch256" brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). L/R = left/ right side of the brain.

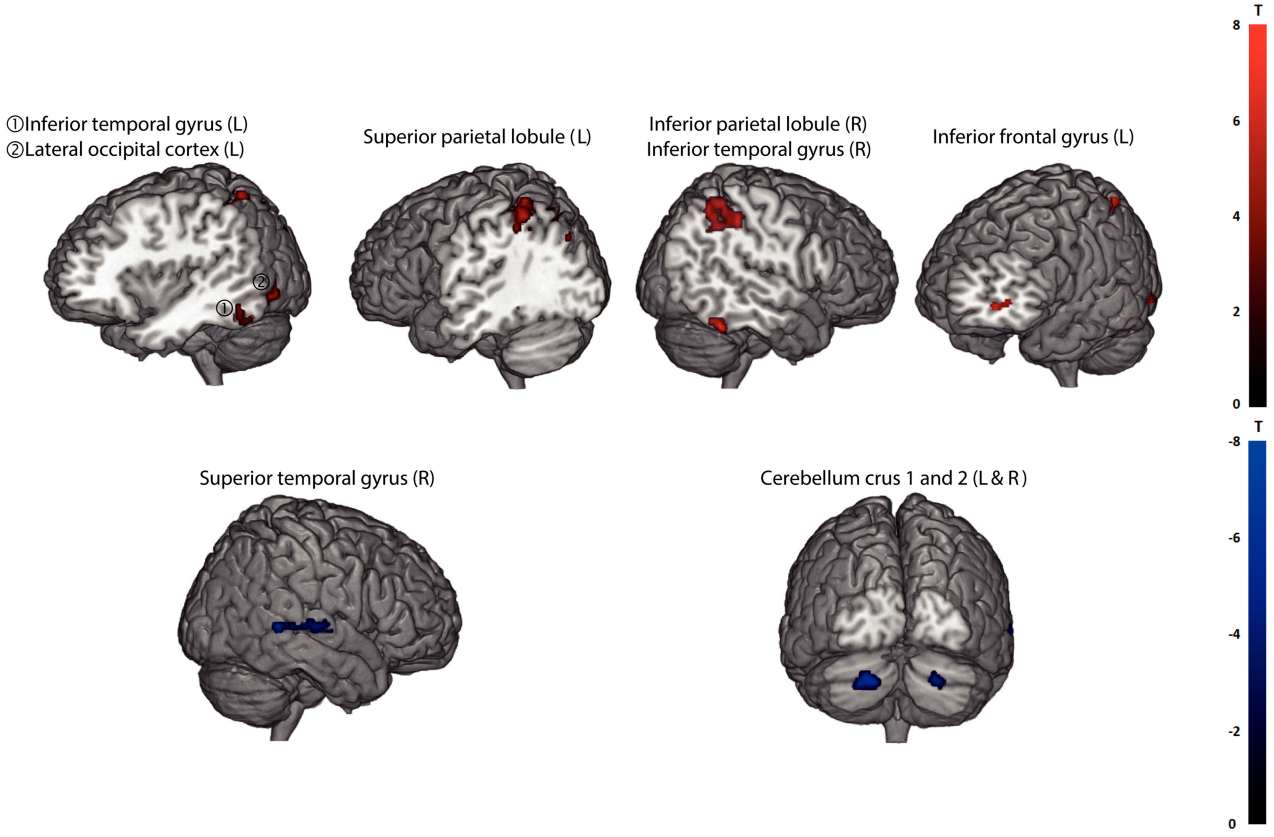

Figure 3. Results from seed-to-voxel functional connectivity (FC) of the left pSTG seed (results of voxel-to-voxel analysis). Higher FC was detected after drum training within left superior parietal lobule, left inferior temporal gyrus, right inferior parietal lobule (angular gyrus and supramarginal gyrus), left and right lateral occipital cortex and left inferior frontal gyrus (upper panel, $P < 0.01$, FWE corrected). A decreased FC was measured after drum training within right superior and middle temporal gyrus (posterior division) and left and right cerebellum crus (lower panel, $P < 0.01$, FWE corrected). Clusters were rendered on the "ch256" brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). L/R = left/ right side of the brain.

Table 2 Functional connectivity of the left pSTG

	Cluster size	Brain areas	MNI coordinates				T_{max}	P_{corr} value
			Side (L/R)	x	y	z		
Post > Pre								
Cluster 1	741	Superior parietal lobule	L	−36	−50	50	7.85	<0.0001
		Lateral occipital cortex	L	−24	−60	34	7.54	
Cluster 2	526	Inferior temporal gyrus	L	−50	−46	−18	6.36	<0.0001
Cluster 3	424	Angular gyrus	R	40	−54	52	6.34	<0.0001
		Supramarginal gyrus	R	42	−36	44	6.24	
		Lateral occipital cortex	R	32	−64	42	5.93	
Cluster 4	103	Inferior temporal gyrus	R	56	−46	−28	8.45	<0.01
Cluster 5	103	Inferior frontal gyrus	L	−30	48	−2	6.43	<0.01
Post < Pre								
Cluster 1	276	Superior temporal gyrus	R	54	−30	4	−6.74	<0.001
		Middle temporal gyrus	R	68	−42	0	−6.54	
Cluster 2	152	Cerebellum crus I and II	L	−18	−76	−36	−6.50	<0.001
Cluster 3	159	Cerebellum crus I and II	R	22	−72	−28	−5.77	<0.001

MNI coordinates (x, y, z) represent peaks within a cluster. Cluster size corresponds to spatial extent (i.e., number of voxels). Correction for multiple comparisons was performed using family-wise error correction at the cluster level.
L/R, left/ right side of the brain.

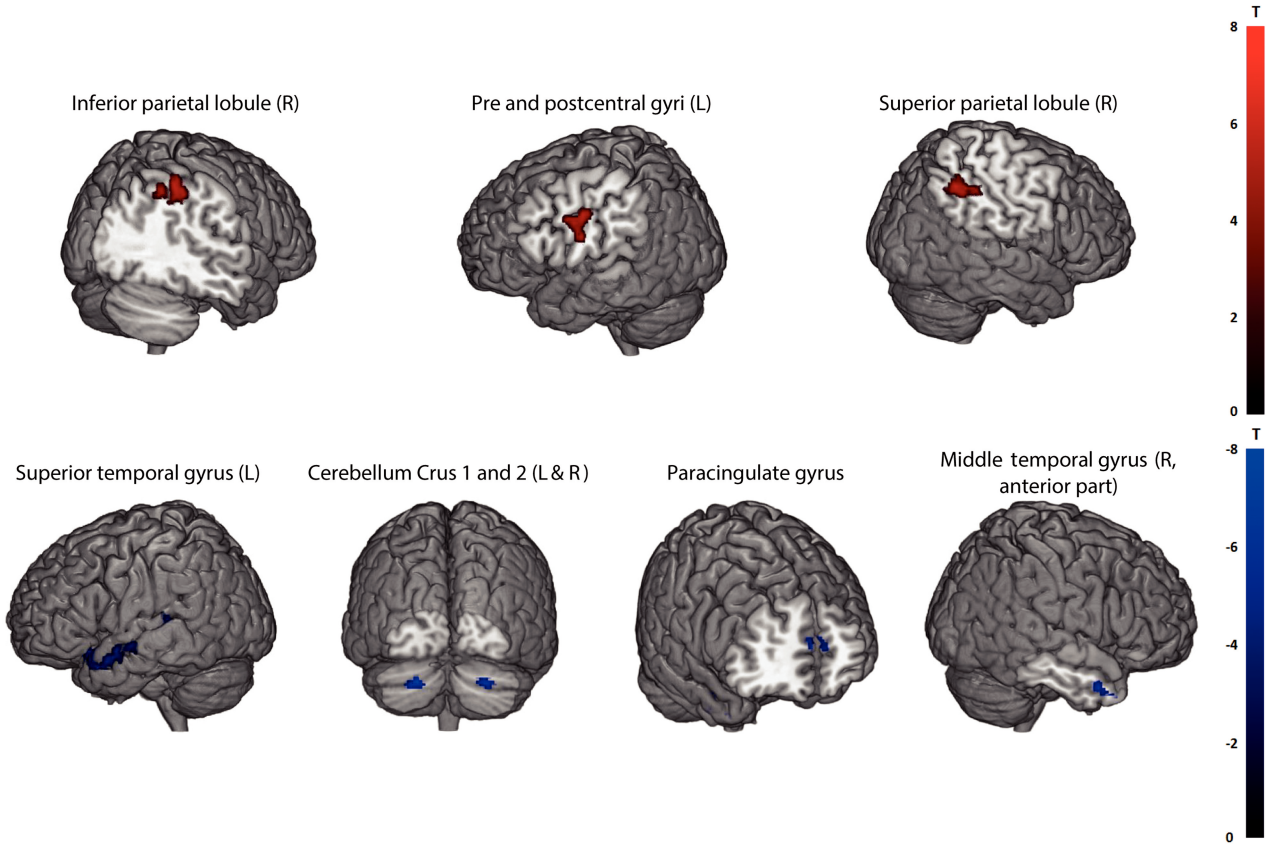

Figure 4. Results from seed-to-voxel functional connectivity (FC) of the right pSTG seed (results of voxel-to-voxel analysis). Higher FC was detected after drum training within right inferior parietal lobule (angular gyrus and superior parietal lobule) and right pre and postcentral gyrus (upper panel, $P < 0.01$, FWE corrected). A decreased FC was measured after drum training within left superior and middle temporal gyrus, left temporal pole, left and right cerebellum crus, paracingulate gyrus and the anterior part of the right MTG. Clusters were rendered on the "ch256" brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). L/R = left/right side of the brain.

improved performance as assessed by the mean number of bars successfully completed for "Green Onions" and "Billie Jean". Interestingly, after 8 weeks, the mean number of bars successfully completed was significantly increased in both groups and for the 2 songs. This increased drum performance in the age-matched control group can be explained by a learning

Table 3 Functional connectivity of the right pSTG

	Cluster size	Brain areas	Side (L/R)	MNI coordinates			T_{max}	P_{corr} value
				x	y	z		
Post > Pre								
Cluster 1	388	Supramarginal gyrus	R	38	−48	38	6.19	<0.0001
		Angular gyrus	R	42	−54	50	6.09	
		Superior parietal lobule	R	32	−54	44	5.73	
Cluster 2	309	Precentral gyrus	L	−48	−10	32	5.67	<0.0001
		Postcentral gyrus	L	−44	−20	32	5.56	
Post < Pre								
Cluster 1	1010	Middle temporal gyrus	L	−52	−24	−12	−7.64	<0.001
		Temporal pole	L	−50	20	−20	−7.53	
		Superior temporal gyrus	L	−58	−32	−2	−7.19	
Cluster 2	137	Cerebellum crus I and II	L	−20	−76	−34	−8.88	<0.001
Cluster 3	134	Cerebellum crus I and II	R	26	−80	−34	−8.28	0.001
Cluster 4	122	Paracingulate gyrus	L	2	50	14	−6.36	<0.01
Cluster 5	116	Middle temporal gyrus	R	48	4	−28	−7.20	<0.01

Note: MNI coordinates (x, y, z) represent peaks within a cluster. Cluster size corresponds to spatial extent (i.e., number of voxels). Correction for multiple comparisons was performed using family-wise error correction at the cluster level.
L/R, left/ right side of the brain.

or familiarization effect since the 2 songs were no longer novel to the participants in both groups. However, the drum group has improved drum performance over and above this simple familiarization effect. Indeed, the progression score was significantly higher for the drum group in comparison with the control group. Moreover, a significant effect of time (i.e., before and after 8 weeks) has been showed in both groups and for the 2 songs, and a significant group (i.e., drummers vs. controls) × time interaction was showed for "Billie Jean". We were unable to utilize more sophisticated measures of drumming performance (such as timing deviations), because we could only evaluate the timing scores from the data that made up the completed bars, since in this population (of novices) there were periods of no playing and patterns that needed to be stopped as they were playing incorrectly. While timing deviation would be a representative statistic for more experienced drummers, this relies on the subject's ability to play the pattern correctly in order to be meaningful. Drum training was also associated with: (1) an increased FC between the posterior part of bilateral pSTG and the rest of the brain (i.e., all other voxels), (2) an increased FC between pSTG and the premotor and motor regions, (3) an increased FC between pSTG and the right parietal lobe which was correlated with drum performance and (4) a decreased FC between regions of the cerebrum and the cerebellum. Moreover, the seed-to-voxel results were confirmed by adopting anatomically defined ROIs. Finally, these results could not be attributed to the MRI session effects (anxiety, novelty of the MRI environment) or to the normal development (Power et al. 2010; Rubia 2013), as no significant FC differences were observed in the age-matched control group.

The whole-brain FC underlying drum training was explored and revealed 2 symmetric brain regions located in the pSTG (see Fig. 2). This result is consistent with previous experiments about the training to play a melody on piano keyboard (Chen et al. 2012), hammering or clapping (Lewis et al. 2005; Galati et al. 2008), and expert drummers (Tsai et al. 2012), which showed that the bilateral pSTG were selectively responsible for action-related sounds. Indeed, the pSTG is a crucial hub of the dorsal auditory streams which is engaged in sensorimotor integration and spatial processing ("how" and "where") (Rauschecker and Tian 2000; Scott et al. 2009) and therefore plays an essential role in auditory–motor transformations ("do-pathway"), which is essential for music processing (Warren et al. 2005; Zatorre et al. 2007).

Interestingly, while using the pSTG as a seed to perform a seed-to-voxel analysis, an increased FC was found between the right pSTG and the left precentral and postcentral gyri including the ventral premotor cortex (vPMC) and the primary motor cortex. The premotor cortex can compute a variety of sensorimotor transformations that are relevant for music and is involved in the motor prediction and production of complex sequences (Zatorre et al. 2007). Specifically, the left vPMC, which might work in tandem with the pSTG (Hickok and Poeppel 2007; Tsai et al. 2012), could be associated with the serial sequence prediction and coupling between hearing music and the execution of a motor programme by the motor cortex, that enable the realization of sensory-cued actions (Zatorre et al. 2007).

The left and right pSTG seed regions showed an increased FC, respectively, with the left and right SPL, a coupling essential in sensorimotor transformation (Hickok and Poeppel 2004; Zatorre et al. 2007). The SPL, which is anatomically connected to the posterior temporal lobe (Kamali et al. 2014), is critical for many sensory and cognitive processes, including sensorimotor (Wolpert et al. 1998) and somatosensory integration, motor learning, spatial perception, mental rotation, visuospatial attention, and memory (Wang et al. 2015). Moreover, it has been involved in the perception of bimanual interaction with an external object (Naito et al. 2008) and the storage of movements and kinematics (Seitz et al. 1997). This appears to be very consistent with the present experiment involving drum training. In the music training framework, the SPL has also been suggested to coordinate the complex spatial and timing components of musical performance (Langheim et al. 2002). After drum training, both pSTG were also more functionally connected with the right inferior parietal lobule (IPL), which comprises of the angular and supramarginal gyri, and the intraparietal sulcus (IPS). Interestingly, the SPL and the IPL cluster, which includes the IPS, are part of the dorsal attention network (Petersen and Posner 2012). The dorsal attention network is involved in the maintenance of spatial priority maps for covert spatial attention, saccade planning, and visual working memory (Vossel et al. 2014). Moreover, our results are consistent with the right hemisphere dominance that has been described

for visuospatial attention (de Schotten et al. 2011). Interestingly, these posterior parietal regions also support mental transformations of acoustic or visual information into motor representations (Warren et al. 2005; Zatorre et al. 2007; Herholz et al. 2015). The increased functional coupling between the bilateral pSTG and the right dorsal attention network might be associated with the improvement of the integration of sensory and motor functions, as the FC of the right parietal lobe cluster was significantly correlated with the improvement in drum performance.

The increased FC between the left pSTG and the inferior frontal gyrus (IFG) corresponds to the ventral auditory streams arising from the primary auditory cortex, and projecting anteriorly from the primary auditory cortex to the IFG along the STG (Scott et al. 2009). This ventral pathway, also known as the what-pathway, is involved in auditory object identification (Leaver and Rauschecker 2010). It is specialized for invariant auditory object properties, which are time-independent, and less related to motor systems (Zatorre et al. 2007). The left seed was more functionally connected with the left inferior temporal gyrus and the lateral occipital cortex. These are part of the ventral visual pathway involved in human object perception and recognition and in the encoding of spatial relationships between subparts of scenes (Grill-Spector and Weiner 2014). This increased FC reflects the audio-visual integration, which has been shown to be crucial in multimodal training (Paraskevopoulos et al. 2012).

Interestingly, both seeds also showed a decreased FC with the bilateral cerebellum (crus I and II). A recent meta-analytic connectivity study identified these 2 cerebellar subregions as part of a cerebellar cluster significantly associated with motor learning, working memory, recitation, and repetition as well as music comprehension and production (Riedel et al. 2015). All integral components involved in learning to play the drums. According to the Marr–Albus–Ito theory on motor learning, cerebellar Purkinje cells (PC) learn to recognize contexts during rehearsal of an action, creating an anticipatory neural state (Marr 1969; Ito 1970; Albus 1971). Climbing fibers innervating the PC further encode possible errors, consequently suppressing the PC synapses involved in such erroneous performance with the help of long-term depression. Once the action has been learned, the occurrence of the context alone is enough to fire the PC to cause the next elemental movement. This increase in efficiency in turn decreases cerebellar activity in the region used, which enables a resource allocation to other areas (Petrini et al. 2011). When such movement involves excitatory output to the cerebral cortex, PC form inhibitory synapses with the deep cerebellar nuclei. As a result, an increase in cerebellar activity would induce a decrease in activity in cortical target regions and vice versa (Vahdat et al. 2011). As a result, the cerebellum is able to integrate and coordinate motor and sensory signals, react quicker and with less error, creating a smooth motor performance. With this increase of efficiency, a decrease of cerebellar activation in regions required for motor learning, music comprehension and production can be expected after drum training.

Both pSTG also showed a decreased FC with the contralateral STG and the right pSTG showed a decreased FC with the ipsilateral anterior part of the MTG. These decreased FC can reflect complex interferences between the ipsilateral and contralateral auditory pathways (Pantev et al. 1986) that can be associated with the synaptic inhibition involved in sound localization (Grothe 2003). In fact, auditory pathways are formed by excitatory and inhibitory neural connections and networks. It is now well-known that music induced lateral inhibition in the human auditory cortex (Pantev et al. 2012). Moreover, reductions in temporal gyrus activity were reported previously for auditory perceptual pitch training (Jäncke et al. 2001) and discrimination training for micromelodies (Zatorre et al. 2012). The right pSTG was also less functionally connected with more frontal regions, such as the paracingulate gyrus, which can reflect interactions in top-down strategies. The frontal regions may be involved in the control of action plans and in the selection and/or inhibition of action chunks. This is particularly important for musical performance, as chunking is defined as the re-organization or re-grouping of movement sequences into smaller sub-sequences during performance, to facilitate the smooth performance of complex movements and to improve motor memory (Zatorre et al. 2007). Those kinds of patterns involving networks with increased and decreased activations or FC have already been described for motor training (Allison et al. 2000; Voelcker-Rehage and Niemann 2013) and in the music literature (Lahav et al. 2007; Petrini et al. 2011; Chen et al. 2012; Pinho et al. 2014). They are furthermore thought to be associated with greater automaticity in cognitive processes (Voelcker-Rehage and Niemann 2013; Beaty 2015).

Finally, the fact that the adult brain is capable of NP modifications, as demonstrated here, highlights the potential of rehabilitation treatments designed to induce plastic changes to overcome impairments due to brain diseases (Wan and Schlaug 2010), which may include stroke, traumatic brain injury, and a range of neuropsychiatric disorders (Cramer et al. 2011). Intriguingly, most regions highlighted by our analyses (IPL, SPL, MTG, and STG) are part of the human mirror neurons system (MNS), which is activated when an individual performs an action and when a similar or identical action is passively observed (Molenberghs et al. 2012). From a clinical perspective, our results could be particularly interesting to consider a drum-based intervention in disorders involving a MNS dysfunction such as in autism spectrum disorders (ASD) (Molnar-Szakacs and Heaton 2012). Drumming with a social partner could then be particularly relevant for individuals with ASD. Previous studies investigating interpersonal body movement synchronization and social processes found that drumming could improve social interaction (Hove and Risen 2009; Kirschner and Tomasello 2009; Yun et al. 2012).

By using additional neuroimaging methods, future studies should also investigate further the functional interplay between cortical and cerebellar regions. Here, DTI tractography and/or structural MRI analyses could explore whether the changes in FC are accompanied by structural changes, which would help illuminate the role of the cerebellum in multimodal action learning. Furthermore, the complex interplay between the left–right hemispheres, as showed in our FC results, should be specifically investigated. Indeed, it is now well-known that musical ability is associated with left–right differences in brain structure and function (Schlaug et al. 1995). However, drummers are unique in that they combine both independent and multilimb coordination when playing, which is necessary for the physical multitasking of drumming and which can lead to complex interhemispheric interactions. Adding an active control group participating in nonmusical motor activities would also help distinguish motor action and higher functions involved in music training. Such an active control condition could consist of learning a new physically demanding multilimb motor sport (such as playing basketball). Finally, adolescence is characterized by changes in brain structure and function, particularly in regions of the cortex, notably the frontal, parietal and temporal regions, that are involved in higher-level cognitive processes (e.g., memory), for which capacity may be increased in adolescence. It has thus been suggested that adolescence might represent a second

"window of opportunity" in brain development (Fuhrmann et al. 2015). However, our results cannot be explained by typical growth trajectories, as volume, thickness, and surface area of the temporal and motor cortices are decreasing in adolescence (Østby et al. 2009). Hence, future experimental studies are needed to compare effect of environment manipulation, such as drum training, in child, adolescent, and older adult groups.

In conclusion, this is the first FC study to compare novice healthy participants before and after an extensive coordinated motor learning such as drumming. An agnostic data-driven approach, i.e., resting-state MVPA, was used to examine the FC of all voxels in the brain, independent of a priori anatomical hypotheses. This method allowed us to highlight the central role of the posterior part of the STG in this task. Moreover, by using the MVPA results as seeds to compute a seed-to-voxel analysis, we showed complex patterns of increased and decreased FC associated with drum training that were partly correlated with the improvement in drum performance. Indeed, as musical training has been shown to modulate unimodal as well as multimodal cortical processing, the seed-to-voxel analyses provide important information on the interaction between the cortical areas involved within the whole network supporting the instrumental performance (Pantev and Herholz 2011). Finally, one can argue that our drum training regimen is a relevant task to highlight the neuroplastic mechanisms involved in motor learning in a naïve population and that drum-based intervention could be relevant to overcome impairments due to brain diseases.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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C. PESPECTIVES ET PROJET SCIENTIFIQUE

De Hermès Trismégiste à Keny Arkana

"Tout ce qu'est en haut, tout est en bas
Tout est unique, tout est semblable
Tout ce qui arrive un jour s'en va
Tout est subtile, tout est grand je crois"

Keny Arkana, *Au milieu du chaos*, 2011

Mes projets de recherche, pour les prochaines années à venir, sont développés dans l'équipe actuelle PSYCHIC du SCALab (UMR 9193, Uni Lille, équipe dirigée par Dr Delphine Pins et Pr Renaud Jardri) et de la future équipe PSY (Plasticity and SubjectivitY) du laboratoire Lille Neuroscience & Cognition. Ces projets s'articulent toujours autour des différents aspects intéressant la neuroplasticité dans les troubles psychiatriques mais avec pour modèle pathologique les pathologies psychiatriques sévères (*serious mental illness*), notamment les formes sévères des troubles de l'humeur et des troubles psychotiques, incluant le syndrome catatonique.

I.Objectiver la subjectivité en psychiatrie

Au cours des quarante dernières années des efforts considérables ont été réalisés pour mieux diagnostiquer les troubles psychiatriques et le développement des classifications internationales (particulièrement la CIM et le DSM) ont permis le développement d'outils et d'échelles standardisés d'évaluation de ces troubles. Il est toutefois important de remarquer que l'immense majorité des manifestations psychiatriques est de nature subjective, malgré l'utilisation de ces outils standardisés. La sémiologie psychiatrique est, en effet, organisée autour de plusieurs dimensions intéressant les dimensions sous-tendant l'expérience humaine quotidienne : les cognitions, l'affectivité, les perceptions, la motivation, la motricité et les relations sociales.

Cependant, à l'heure actuelle, plusieurs moyens technologiques permettraient d'objectiver la plupart des manifestations psychiatriques : capteurs sophistiqués, caméra, algorithmes d'analyse des émotions faciales, développement de l'intelligence artificielle... Pour recueillir des informations cliniquement pertinentes, le smartphone semble être un outil de choix. En effet, ces appareils, petits, puissants et surtout très répandus permettent de collecter des informations ayant, de façon intuitive, un intérêt clinique certain : activité physique, localisation, relations sociales. Le terme de « *digital phenotype* » (Jain et al. 2015) a ainsi été proposé dans la littérature pour évoquer les différentes mesures du comportement humain grâce aux différents capteurs des smartphone : interaction avec le clavier, caractéristiques de la voix, du discours, des relations sociales. Au-delà de ces données, un smartphone permet aussi de collecter des informations plus complexes relatives au contenu et à la prosodie du discours, aux mots tapés par les sujets, voire d'évaluer les facultés cognitives en évaluant la façon dont un individu tape sur un clavier et fait défiler son écran. Ces informations sont cliniquement pertinentes et pourraient permettre de détecter les rechutes, les symptômes précoces ou encore les idées et comportements suicidaires (Insel 2017; Simon et al. 2018).

La dépression sévère est un champ d'étude particulièrement adapté à la création de cet outil permettant de recueillir des informations pertinentes cliniquement. S'intéresser à la dépression sévère

permettra d'évaluer et d'analyser de façon objective 1) l'activité physique (nombre de pas et fréquence cardiaque), 2) évaluation et analyse de la voix (tonalité, prosodie), 3) vitesse d'exécution, 4) émotions et motricité du visage, 5) comportement social. Au-delà de l'objectivation des signes et symptômes psychiatriques, les objectifs de ce projet correspondent naturellement à l'amélioration de la précision des diagnostics psychiatriques et à la prédiction des rechutes, fréquentes dans ces pathologies.

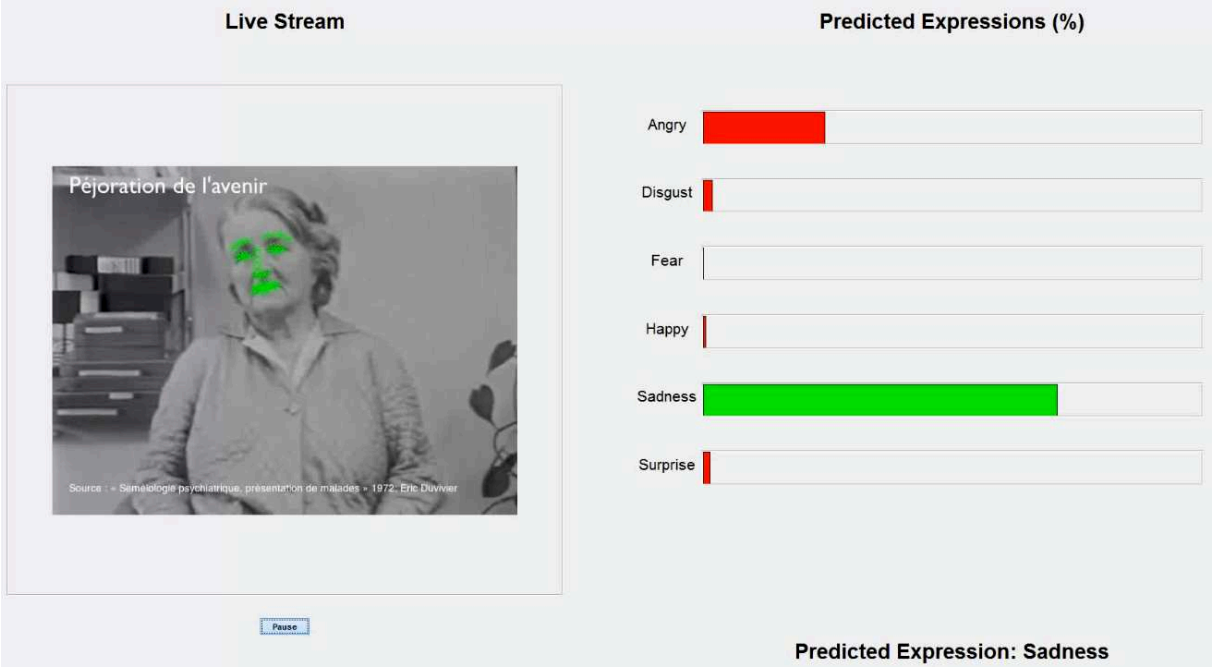

Figure 5. Exemple d'analyse des émotions faciales chez un sujet souffrant de dépression (d'après (Kacem et al. 2018)).

Ce travail a déjà débuté et sera développé au cours des prochaines années, en collaboration avec le Pr. Mohamed Daoudi, professeur d'informatique, chercheur au laboratoire CRISTAL, et spécialiste en intelligence artificielle (*machine learning* et *pattern recognition*). Plusieurs de ses travaux ont déjà analysé par ordinateur les expressions faciales de sujets sains mais aussi de sujets souffrant de dépression (Kacem et al. 2018).

Pour compléter cette approche d'analyse du visage, nous avons encadré cette année 4 étudiants de cinquième année d'école d'informatique (école IMT Lille-Douai) pour pouvoir extraire et analyser toutes les informations pertinentes possibles à partir des différents capteurs de smartphone. Par ailleurs, au cours des prochains mois, une étude de cas chez un patient en cours de traitement va

être réalisée. Dans cette étude, des points de repères seront extraits du visage d'un patient en cours de traitement. Cette extraction est rendue anonyme par la méthode de *landmarks* développée dans ce cadre (Kacem et al. 2018). Cette étude de cas permettra d'objectiver les changements d'expressions faciales des émotions chez un patient en cours de traitement. Ces changements seront comparés à des échelles standardisés réalisées de façon hebdomadaires. L'hypothèse de cette étude de cas, unique à l'heure actuelle, est que des changements seront visibles de façon plus précoce avec l'analyse des émotions faciales plutôt que grâce aux échelles traditionnelles. D'autres types de mesures (nombre de pas, tonalité de la voix, activité électro-dermale), viendront aussi progressivement compléter ce type d'étude de cas. Après avoir ancré ces travaux grâce à des publications de faisabilité et *case reports*, cet axe sera développé au cours des prochaines années et permettra d'encadré des étudiants de différents niveaux (M1, M2 et thèse) au cours de son développement. Des financements spécifiques « santé et nouvelles technologies » sont en cours de mobilisation.

II. Approche multi-échelle des facteurs environnementaux des pathologies psychiatriques sévères

Depuis plusieurs années, l'étude de l'implication des facteurs environnementaux se développe en psychiatrie sur le plan épidémiologique mais également dans le contexte d'interaction avec le système nerveux (exemple de la neuroplasticité) ou encore des facteurs génétiques (Tost, Champagne, et Meyer-Lindenberg 2015). L'environnement est alors défini comme « tout ce qui est différent du gène » et peut donc se conceptualiser grâce à une approche multi-échelle (cf. figure ci-dessous). Ces considérations permettent une approche afin d'étudier l'interaction entre les facteurs environnementaux et les facteurs biologiques (génétiques) à plusieurs échelles : du gène au à l'épidémiologie ainsi que d'inclure l'étude des aspects thérapeutiques, inhérents à la définition de la résistance aux traitements. Plusieurs projets seront développés dans cet axe.

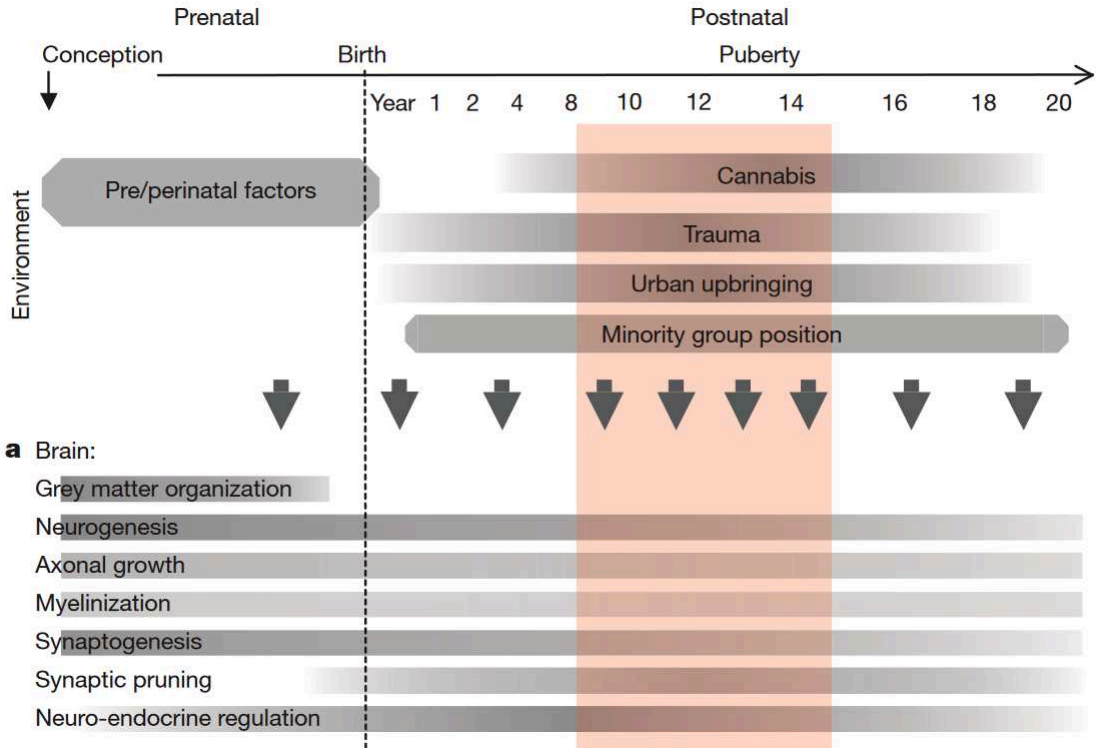

Figure 6 Exemple de différents facteurs environnementaux de différentes échelles pouvant interagir avec le système nerveux différemment à différents moments du développement et être associés à différents troubles psychiatriques (d'après (van Os, Kenis, et Rutten 2010)).

1) Epidémiologie des facteurs environnementaux des pathologies psychiatriques sévères

a) Comparaison des facteurs de risque environnementaux entre troubles psychotiques et troubles de l'humeur

La schizophrénie et le trouble bipolaire sont souvent considérés comme faisant partie du même continuum notamment en lien avec une dérégulation dopaminergique qui serait commune. Cependant, il semble que les facteurs environnementaux associés à ces troubles soient différents, notamment la migration, impliquée dans le modèle de défaite sociale, qui serait spécifique à la schizophrénie et non retrouvée comme associée aux troubles bipolaires (Demjaha, MacCabe, et Murray 2012). Ce projet correspond à la comparaison directe des facteurs environnementaux chez des sujets souffrant de schizophrénie et de trouble bipolaire grâce à l'analyse de bases de données épidémiologiques ayant déjà fait l'objet de publication (base SMPG : Santé Mentale en Population Générale, regroupant plus de 35 000 sujets interrogés). Cette étude sera réalisée au cours du premier semestre 2019 en collaboration avec une équipe parisienne (Inserm, U955, team 15, Créteil, 94000, France) à travers l'encadrement de Baptiste Pignon, actuellement en première année de thèse, avec qui plusieurs travaux épidémiologiques ont déjà été réalisés.

b) Facteurs de risques environnementaux des dépressions avec caractéristiques psychotiques

D'autre part, les liens entre ces dimensions « troubles de l'humeur » et « troubles psychotiques » peut s'interroger en s'intéressant également à la dépression. Il existe en effet peu d'étude concernant les dépressions associées à des symptômes psychotiques, notamment en population générale. Cette question sera abordée par une étude de la même base dans le cadre de l'encadrement de la thèse du Dr Victoire Bénard, deuxième année de thèse, au cours du deuxième semestre 2019. Ce travail sera aussi accompagné par la mise en place d'une cohorte de patients souffrant de dépression avec caractéristiques psychotiques.

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Environment risk factors have different impact on bipolar and psychotic disorders: an analysis of MHGP survey

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Dear Editor

Dykxhoorn *et al.* (2018) recently analysed the Swedish registers and calculated the incidence of (i) affective and non-affective psychotic disorders and (ii) non-psychotic bipolar disorder, according to migrant status among residents born between 1982 and 1996. They found that all psychotic disorders were significantly elevated among first- and second-generation migrants (1GM and 2GM), including schizophrenia and schizoaffective disorders, affective psychotic disorder and other non-affective psychotic disorders. Moreover, the incidence of non-psychotic bipolar disorder was significantly reduced among 1GM and non-significantly different among 2GM. Authors concluded to a specific effect of the migrant-related exposures on the risk of psychotic disorders as no effects were observed for non-psychotic bipolar disorders.

We read with interest this study that adds to the literature highlighting continuities and discontinuities between psychotic and bipolar disorders. Based on clinical overlaps and multi-scale similarities, some authors have argued for going beyond the Kraepelinian dichotomy and for pooling in a single entity these two diagnoses of psychotic and bipolar disorders (Guloksuz and van Os, 2018). Interestingly, several studies have suggested the involvement of partially shared and partially different environmental exposures between these disorders (Demjaha *et al.*, 2012).

To disentangle these shared and specific environmental risk factors, studies that focus on different risk factors and different disorders are required. Moreover, these studies should also consider separately psychotic bipolar disorders, i.e. a phenotype considered as intermediate between non-psychotic bipolar disorder and psychotic disorder. Mental Health in General Population (MHGP) survey offers such an opportunity. Moreover, it allows for the first time to study the third-generation of migrants (3GM). Thus, the aim of the present study was to compare the influence of different environment risk factors [migrant status, history of trauma, substance use disorders (SUDs) and alcohol use disorders (AUDs)] on the prevalence of psychotic disorders, and of psychotic and non-psychotic bipolar disorder in the MHGP survey.

The MHGP survey, conducted by the World Health Organization Collaborating Centre, interviewed 38 694 subjects selected by a quota sampling method in France between 1999 and 2003 (47 sites). For each subject, the *Mini International Neuropsychiatric Interview* (MINI) was used to screen for 10th International Classification of Diseases defined psychiatric disorders in the general population. To define bipolar disorders with and without psychotic symptoms, the seven psychotic symptoms of the psychotic disorders section were used. Further details on MHGP survey and diagnoses procedures are available elsewhere (Amad *et al.*, 2013; Pignon *et al.*, 2017, 2018).

To compare specifically subjects with psychotic disorders to those with bipolar disorders, subjects with both diagnoses were excluded. Four groups were defined: psychotic disorders, bipolar disorders with psychotic symptoms (i.e. psychotic bipolar disorders), non-psychotic bipolar disorders and 'control' subjects without psychotic or bipolar disorders. We performed logistic regression analyses to compare the different risk factors between the four groups, defining the control group as reference. We controlled these analyses for age, sex, and educational, income and marital status. All statistical analyses were performed using R software version 3.1.0 (http://www.R-project.org).

Of the 38 694 individuals interviewed, 140 subjects were excluded because of dual diagnoses of bipolar and psychotic disorders (0.36% of the total sample). At the end, 474 subjects with bipolar disorders, including 293 without psychotic symptoms (0.76%) and 181 with psychotic symptoms (0.47%), and 933 subjects with psychotic disorders (2.42%) were analysed.

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Table 1. Logistic regression analyses* to compare subjects with psychotic and non-psychotic bipolar disorder, and psychotic disorders, to subjects without bipolar or psychotic disorder

	Controls ($n = 37\,147$) (reference)		Non-psychotic bipolar disorder ($n = 293$)						Psychotic bipolar disorder ($n = 181$)						Psychotic disorder ($n = 933$)					
	N	%	*N*	%	OR	95% CI −	95% CI +	*p*	*N*	%	OR	95% CI−	95% CI +	*p*	*N*	%	OR	95% CI−	95% CI +	*p*
Age band																				
18–29 years	9216	24.8	114	38.9	**3.76**	**2.10**	**6.75**	**<0.001**	46	25.4	1.80	0.95	3.40	0.072	298	31.9	**1.44**	**1.09**	**1.92**	**0.011**
30–44 years	10 578	28.5	108	36.9	**3.93**	**2.28**	**6.77**	**0.002**	72	39.8	**2.53**	**1.46**	**4.38**	**<0.001**	302	32.4	**1.82**	**1.41**	**2.35**	**<0.001**
45–59 years	8121	21.9	48	16.4	**2.40**	**1.37**	**4.23**	**0.002**	35	19.3	1.52	0.86	2.69	0.153	191	20.5	**1.77**	**1.37**	**2.29**	**<0.001**
60+years (reference)	9232	24.9	23	7.8	–	–	–	–	28	15.5	–	–	–	–	142	15.2	–	–	–	–
Gender																				
Male (reference)	17 057	45.9	172	58.7	–	–	–	–	106	58.6	–	–	–	–	470	50.4	–	–	–	–
Female	20 090	54.1	121	41.3	0.80	0.62	1.03	0.372	75	41.4	0.75	0.55	1.03	0.073	463	49.6	1.08	0.94	1.25	0.255
Education level																				
No education – elementary level	8959	24.1	49	16.7	1.21	0.80	1.83	0.372	42	23.2	**1.70**	**1.03**	**2.80**	**0.037**	192	20.6	1.10	0.88	1.39	0.406
Secondary level	18 177	48.9	170	58	1.15	0.86	1.53	0.349	97	53.6	1.31	0.89	1.92	0.164	505	54.1	1.10	0.93	1.30	0.43
University level (reference)	10 011	26.9	74	25.3	–	–	–	–	42	23.2	–	–	–	–	236	25.3	–	–	–	–
Marital status																				
Married (reference)	20 322	55.2	112	38.2	–	–	–	–	79	43.9	–	–	–	–	348	37.5	–	–	–	–
Never married	10 120	27.5	126	43	1.25	0.92	1.72	0.159	62	34.4	**1.55**	**1.03**	**2.33**	**0.036**	402	43.3	**1.75**	**1.46**	**2.09**	**<0.001**
Separated	2971	8.1	48	16.4	**2.43**	**1.69**	**3.50**	**<0.001**	27	15.0	**2.22**	**1.40**	**3.55**	**<0.001**	118	12.7	**1.75**	**1.40**	**2.19**	**<0.001**
Widowed	3430	9.3	7	2.4	0.76	0.32	1.77	0.520	12	6.7	1.57	0.77	3.20	0.212	61	6.6	1.21	0.87	1.67	0.258
Income level[a]																				
Low	13 685	37.9	145	51.2	1.59	1.10	2.29	0.012	68	38.0	0.79	0.50	1.24	0.298	482	53.4	1.63	1.32	2.01	<0.001
Medium	14 589	40.4	93	32.9	1.05	0.73	1.25	0.777	75	41.9	0.94	0.62	1.42	0.760	279	30.9	1.02	0.82	1.25	0.908
High (reference)	7846	21.7	45	15.9	–	–	–	–	36	20.1	–	–	–	–	141	15.6	–	–	–	–
Migrant status																				
Native (reference)[b]	27 722	74.6	200	68.3	–	–	–	–	135	74.6	–	–	–	–	593	63.6	–	–	–	–
1GM	1943	5.2	16	5.5	0.93	0.55	1.59	0.793	14	7.7	1.41	0.80	2.46	0.232	75	8.0	**1.62**	**1.26**	**2.08**	**<0.001**
2GM	3944	10.6	39	13.3	0.88	0.61	1.27	0.491	16	8.8	0.70	0.41	1.18	0.181	131	14.0	**1.24**	**1.02**	**1.52**	**0.032**
3GM	3538	9.5	38	13	1.02	0.71	1.46	0.908	16	8.8	0.78	0.46	1.32	0.350	134	14.4	**1.43**	**1.17**	**1.74**	**<0.001**

History of trauma																			
Yes	10 637	28.7	147	50.2	**2.15**	**1.69**	**2.74**	**<0.001**	68	37.8	**1.41**	**1.03**	**1.92**	**0.030**	474	49.2	**2.33**	**2.04**	**2.67**	**<0.001**
No (reference)	26 742	71.3	146	48.8	-	-	-	-	112	62.2	-	-	-	-	459	50.8	-	-	-	-
Alcohol use disorders																				
Yes	1452	3.8	50	17.1	**2.17**	**1.53**	**3.08**	**<0.001**	30	16.6	**3.47**	**2.24**	**5.36**	**<0.001**	121	13.0	**2.03**	**1.62**	**2.55**	**<0.001**
No (reference)	35 695	96.1	243	82.9	-	-	-	-	151	83.4	-	-	-	-	812	87.0	-	-	-	-
Substance use disorders																				
Yes	866	2.3	51	17.4	**3.90**	**2.70**	**5.62**	**<0.001**	10	5.5	1.25	0.63	2.50	0.520	104	11.1	**2.58**	**2.01**	**3.33**	**<0.001**
No (reference)	36 281	97.7	242	82.6	-	-	-	-	171	94.5	-	-	-	-	829	88.9	-	-	-	-

1GM, 2GM and 3GM: first-, second- and third-generation of migrants; 95% CI− and 95% CI+: 95% confidence interval lower and upper limits; OR: odds ratio; *p*: *p*-value.
In bold: the significant ($p < 0.05$) relationships.
[a]Monthly income levels: low <€1.650/household; medium: €1.650–€3.200/household; high: >€3.200/household.
[b]Subject who was born in and whose parents and grandparents were born in metropolitan France.
*Analyses adjusted for age, sex, and educational, income and marital status.

Table 1 shows sociodemographic and clinical characteristics of the four groups. The rates of migrants (1GM, 2GM and 3GM) were higher among subjects with psychotic disorders (ORs between 1.52 and 2.08), in contrast to the rates of migrants in psychotic and non-psychotic bipolar disorders groups. Rates of subjects with a history of trauma were higher in the three groups (ORs between 1.41 and 2.33). Likewise, for AUDs (ORs between 2.03 and 3.47). The rates of subjects with SUDs were higher among the subjects with non-psychotic bipolar disorders (OR = 3.90) and among subjects with psychotic disorders (OR = 2.58).

These results confirm the Demjaha *et al.* (2012) observation suggesting that, between bipolar and psychotic disorders, environment exposures involved are partially shared and partially different. Our results are also consistent with Dykxhoorn *et al.*'s study on the different effects of migrant-related exposures on the two types of disorders: 1GM and 2GM status were associated with increased incidence of psychotic disorders and not with non-psychotic bipolar disorders. However, unlike Dykxhoorn *et al.*, we did not find any association between migrant status and the frequency of psychotic bipolar disorders. Interestingly, a recent meta-analysis of six studies considering the risk of mood disorder among migrants did not find any association between 1GM status and bipolar disorder (Mindlis and Boffetta, 2017). Our study also presents data concerning 3GM, also showing increased rates of psychotic disorders but not bipolar disorders, including those with psychotic symptoms, among migrants.

The history of trauma has been widely studied in the scientific literature that shows an increased risk associated with both psychotic and bipolar disorders (Carr *et al.*, 2013), as found in our study. Finally, we did not find different impact of either AUDs or SUDs on psychotic or bipolar disorders prevalences. This is in line with actual knowledge of an increased risk for both disorders regarding SUDs that could represent an unspecific risk factor of both bipolar and psychotic disorders (Demjaha *et al.*, 2012).

Of note, several other environment factors are known to have a different impact on bipolar and psychotic disorders. Urbanicity, one of the oldest and best acknowledged risk factor of psychotic disorders (March *et al.*, 2008), has a slight or null effect on the risk of bipolar disorder (Mortensen *et al.*, 2003). Studies of urban neighbourhood variations of incidence and prevalence also showed different patterns for affective and non-affective psychotic disorders (March *et al.*, 2008). Obstetric complications, advanced paternal age or birth in winter are more or less in the same situation (Demjaha *et al.*, 2012).

Overall, the MHGP survey allowed to compare risk factors across a continuum ranging from bipolar disorder without psychotic features to psychotic disorders and observed the involvement of shared and specific environmental risk factors in these disorders with or without psychotic symptoms.

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2) Approche multi-échelle des traitements physiques utilisés en psychiatrie

a) Méta-recherche sur les traitements par neuromodulation utilisés dans les situations de résistance aux traitements

La neuromodulation correspond à l'induction de modifications neuroplastiques permettant la modification de l'activité pathologique de certains neurones ou circuits neuronaux afin de corriger leur dysfonctionnement et d'obtenir un effet thérapeutique (Micoulaud-Franchi, Fond, et Dumas 2013). En psychiatrie, la neuromodulation est devenue une alternative dans la prise en charge thérapeutique dans des situations de résistance au traitement conventionnel.

Une des méthodes les plus diffusées au cours des dernières années correspond à la stimulation magnétique transcrânienne répétée (rTMS). L'efficacité de ce traitement reste débattue (Amad, Naudet, et Fovet 2019). Ce projet utilise des méthodes statistiques issues de la méta-recherche pour interroger l'efficacité rTMS dans les situations neuropsychiatriques sévères ou résistantes. Un premier travail concernant l'ensemble de la littérature neuro-psychiatrique, issu d'une collaboration avec les équipes de Rennes et l'équipe METRICS de Stanford, est en cours de finalisation et sera publié courant 2019. Courant 2019 et 2020, ce travail sera être décliné trouble par trouble à travers l'encadrement d'étudiants.

b) Epidémiologie de l'électro-convulsivo-thérapie en France et parcours de soins

L'électro-convulsivo-thérapie (ECT), traitement physique de neuromodulation, correspond au traitement le plus efficace des troubles de l'humeur, notamment de la dépression sévère et résistante. Son utilisation est limitée, notamment en France, en raison de la stigmatisation dont ce traitement est victime mais aussi en rapport avec des organisations souvent complexes entre services de psychiatrie et service d'anesthésie. Néanmoins, ce traitement a montré son efficacité dans la prise en charge des formes sévères d'épisodes dépressifs caractérisés et de la dépression résistante. Le recours à l'ECT intervient probablement trop tardivement dans le parcours de soin du patient souffrant de dépression et plus particulièrement de dépression résistante alors qu'il s'agit d'un traitement vraisemblablement incontournable de leur parcours de soin. Les objectifs de ce projet sont : 1) évaluer le parcours de soin

des patients déprimés dans la région des Hauts de France et notamment le recours aux ECT, 2) appréhender les facteurs cliniques, médicamenteux et médicaux intervenant dans la décision de traiter par ECT, 3) déterminer les conséquences de l'ECT sur le parcours des patients.

Il s'agit d'une étude épidémiologique, de cohorte, rétrospective et multicentrique nationale avec un focus sur les Hauts de France, se basant sur les données du PMSI-MCO (Programme de Médicalisation des Systèmes d'Information en médecine, chirurgie, obstétrique) et RimP (Recueil d'information médicalisée en psychiatrie). Les patients déprimés sont identifiés à l'aide de l'algorithme proposé par la CnamTS. Les résultats de l'étude permettront de développer et implanter un parcours de soins intégré et adapté à la prise en charge des patients présentant une dépression majeure depuis les soins ambulatoires jusqu'à l'hospitalisation, au retour à domicile et à la reprise du travail. Ce travail sera réalisé avec Alice Demesmaecker à partir de novembre 2019 dans le cadre de sa première année de thèse de science financée dans le cadre de son post-internat. Ce travail devrait s'accompagner de l'organisation d'un lien entre les différents centres d'ECT des Hauts de France entre eux à visée clinique mais permettant également de recueillir des informations utilisables sur le plan de la recherche.

Par ailleurs, sur le plan biologique, plusieurs hypothèses sont actuellement discutées pour expliquer le mécanisme d'action et l'efficacité de l'ECT, comme une activation importante du système GABAergique ou encore une relance des mécanismes neuroplastiques. Pourtant ces mécanismes restent hypothétiques et le mécanisme d'action de ce traitement restent largement méconnus. Ce projet s'intéressera à la compréhension de l'efficacité de l'ECT à un niveau génétique, épigénétique et en imagerie cérébrale via la participation à un consortium international en cours de création avec l'*Institute of Psychiatry* et le *Center for Neuroimaging Science* du *King's College* à Londres. Ce consortium verra le jour au cours de 2019/2020 mais ne sera effectif et ne permettra d'étudier des données qu'au cours de 2020-2021. Sur le plan local, la participation dans ce travail sera en partie tributaire de la réussite au projet de création d'une unité dédiée à l'ECT et du réseau régional dont les

négociations sont en cours et sont très encourageantes. La possibilité de co-encadrer un étudiant en thèse de science sur cette thématique avec le *King's College* de Londres est en cours de discussion.

3) Prédiction de la réponse au traitement et catatonie : approche pharmacogénétique et d'imagerie cérébrale

Ce projet s'inscrit en conceptualisant la pharmacogénétique comme une situation particulière d'interaction gène x environnement dans lequel l'environnement n'est autre que le médicament.

La catatonie est un syndrome retrouvé chez 10 à 15% des patients hospitalisés en psychiatrie dont le diagnostic repose sur le repérage de 3 critères sur 12 selon le DSM-5. Le tableau clinique comprend principalement des signes moteurs (difficulté au démarrage et à l'arrêt du mouvement) et des signes frontaux (attitudes d'aimantation, échophénomènes). Les étiologies peuvent être psychiatriques (troubles de l'humeur, schizophrénie) ou non psychiatrique (systémique, endocrinologiques, cancéreuses ou métaboliques, etc.). La prise en charge implique un bilan clinique et paraclinique (biologie et imagerie cérébrale) de recherche étiologique et de complications et un traitement rapide (mortalité atteignant 50% en l'absence de traitement). Le traitement de référence est le lorazépam (benzodiazépine) titré progressivement en fonction de la réponse thérapeutique sur quelques jours jusqu'à la posologie maximale consensuelle de 24 mg par jour. 70% des patients répondent positivement au traitement par benzodiazépines. En cas d'échec (non réponse malgré des posologies atteignant 24 mg/j, soit 30% des patients), le traitement de recours est l'électro-convulsivo-thérapie. Des variants pharmacogénétiques peuvent modifier le métabolisme du lorazépam (par ex. l'allèle UGT2B15*2 le ralentit).

L'objectif principal de ce travail est d'étudier le lien entre la réponse clinique au lorazépam, les concentrations plasmatiques résiduelles en lorazépam après 72h de posologie fixe (correspondant au plateau d'équilibre du médicament à partir duquel la concentration sanguine est stable) et l'existence de polymorphismes génétiques modifiant le métabolisme du lorazépam. L'hypothèse est que les patients non répondeurs ont des concentrations sanguines en lorazépam abaissées en lien avec un profil génétique de métabolisation rapide.

Evaluer les facteurs prédictifs de la réponse au traitement permettraient d'identifier précocement et précisément les patients non répondeurs afin d'adapter leur prise en charge en première intention. Des IRM cérébrales avant et après traitement seront réalisées également chez ces patients afin de rechercher des différences anatomiques ou fonctionnelles de repos entre les répondeurs et les non-répondeurs mais également avant et après le traitement. Les images issues de l'IRM (IRM initiale et à 3 mois) seront également combinées aux données biologiques (dosage de benzodiazépines et génotypage) et inclues dans un classificateur (Support Vector Machine), pour évaluer la valeur prédictive des différentes modalités combinées.

Ces aspects de prédiction seront aussi analysés en collaboration avec le l'*Institute of Psychiatry* et le *Center for Neuroimaging Science* du *King's College* à Londres. Un premier financement spécifique a été obtenu pour ce projet (financement GIRCI) qui débutera courant 2019 et se poursuivra sur plusieurs années avec la mise en place d'une cohorte de patients catatoniques suivis dans le temps. Ce travail permettra l'encadrement de plusieurs étudiants de différents niveaux. Des études complémentaires vont également progressivement se greffer à ce projet, notamment l'étude de l'activité électrodermale des patients catatoniques grâce à un bracelet (EMPATICA) permettant de capter ces données de façon continue et passive pour le patient. Ce dernier travail est en collaboration avec le Dr Fabien D'Hondt et un étudiant de M1 va être encadré sur ce travail (Thibaut Denis). Un article de revue complète sur tout ce qui a été publié sur l'imagerie de la catatonie est également en cours d'écriture avec le Dr Alexandre Haroche, encadré initialement pour sa thèse de médecine, et est actuellement en cours de soumission.

III.L'adaptation plastique à la pathologie

Les troubles psychiatriques partagent, outres les symptômes communs à plusieurs troubles, les mêmes caractéristiques évolutives, c'est-à-dire qu'ils ont tendance à la chronicité et à la répétition de leurs épisodes. Les troubles psychiatriques sont associés à des taux importants de rechute et chaque épisode augmente la probabilité de futurs épisodes. Cette évolution est associée à une réduction de la probabilité de réponse au traitement au plus la maladie progresse.

Ces différents aspects, de chronicité et d'évolution longitudinale, sont actuellement étudiés à travers le concept de neuroprogression et de nombreux travaux mettent ainsi en évidence des modifications spécifiques associées à l'évolution dans le temps des maladies : pertes de substance grise, des diminutions de connectivité cérébrale et à une inflammation chronique. Cependant, il semble nécessaire de penser également la nature bidirectionnelle des modifications neuroplastiques, notamment à la lumière des concepts de l'économie énergétique cérébrale. En effet, il apparaît que pour rester stable le cerveau compenserait très vraisemblablement ces différentes pertes de connectivité par des augmentations de connectivité dans d'autres régions.

Un premier projet théorique reprend la littérature mettant en évidence des gains de volume de certaines régions cérébrales et des augmentations de connectivité en lien avec l'évolution dans le temps des maladies et intègre ces données avec les concepts d'économie énergétique du cerveau. Cet article vient d'être accepté dans la revue *The Neuroscientist* (cf. ci-dessous). Sur le plan expérimental, cette hypothèse sera testée, afin de mettre en évidence de façon transdiagnostique, des patterns de connectivité communs entre différents troubles en lien avec l'évolution dans le temps des maladies et l'adaptation plastique à la pathologie, plutôt que des modifications en lien avec la symptomatologie des différents troubles. Cette hypothèse est actuellement en train d'être testée sur des troubles neurologiques par une équipe de recherche de l'*Imperial College* de Londres.

Ce projet ambitieux nécessite des avancées techniques importantes concernant d'une part les analyses longitudinales et d'autre part pour mettre en évidence des points communs entre les différents réseaux plutôt que des différences. Concernant les données, plusieurs consortium internationaux existent et mettent à disposition des données transdiagnostiques bien documentées. Sur le plan pratique, ce travail s'inscrirait idéalement dans le cadre d'un projet de postdoc dont le financement devrait être obtenu au cours des deux prochaines années.

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Plastic Adaptation to Pathology in Psychiatry: Are Patients with Psychiatric Disorders Pathological Experts?

Ali Amad[1,2,3], Paul Expert[1,4,5,6], Louis-David Lord[7], Thomas Fovet[2,3], and Pierre A. Geoffroy[8,9]

Abstract

Psychiatric disorders share the same pattern of longitudinal evolution and have courses that tend to be chronic and recurrent. These aspects of chronicity and longitudinal evolution are currently studied under the deficit-oriented neuroprogression framework. Interestingly, considering the plasticity of the brain, it is also necessary to emphasize the bidirectional nature of neuroprogression. We review evidence highlighting alterations of the brain associated with the longitudinal evolution of psychiatric disorders from the framework of neuroplastic adaptation to pathology. This new framework highlights that substantial plasticity and remodeling may occur beyond the classic deficit-oriented neuroprogressive framework, which has been associated with progressive loss of gray matter thickness, decreased brain connectivity, and chronic inflammation. We also integrate the brain economy concept in the neuroplastic adaptation to pathology framework, emphasizing that to preserve its economy, i.e. function, the brain learns how to cope with the disease by adapting its architecture. Neuroplastic adaptation to pathology is a proposition for a paradigm shift to overcome the shortcomings of traditional psychiatric diagnostic boundaries; this approach can disentangle both the specific pathophysiology of psychiatric symptoms and the adaptation to pathology, thus offering a new framework for both diagnosis and treatment.

Keywords

neuroplasticity, neuroprogression, psychiatric disorders, brain economy, severe mental illness, biomarkers

Introduction

The prevalence, severity, and overall burden of morbidity and mortality represented by psychiatric disorders reflect an urgent global public health priority (Whiteford and others 2013). However, to date, objective measures of psychopathology and biomarkers that reliably delineate normal from disease states, or one disease state from another, are still lacking (Akil and others 2010; Krystal and State 2014). Indeed, for the past 40 years, genomics, neurobiology, cognitive neuroscience, neuroimaging, and pharmacology development have challenged the psychiatric diagnostic nosology boundaries (Krystal and State 2014). Interestingly, the transdiagnostic approach appears as a paradigm shift in the understanding of psychiatric disorders. Indeed, nosological systems, such as the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) and *ICD-10* (*International Classification of Diseases*, 10th Revision), define the different psychiatric disorders as distinct, independent, and categorical constructs (Krueger and Eaton 2015). However, psychiatric diagnosis has always been challenging due to the complexity and heterogeneity of the symptoms that may occur in a particular disorder and the potentially confusing comorbidities with other psychiatric disorders (McHugh 2005).

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For several years, the transdiagnostic approach has been developed by focusing on certain clinical dimensions or symptoms such as psychosis (van Os and Reininghaus 2016), anhedonia (Zhang and others 2016), or compulsivity (Gillan and others 2016), with the objective of cutting across existing categorical diagnoses and discerning possible commonalities that may highlight new neurobiological or therapeutic avenues. However, beyond the transdiagnostic approach of symptoms, psychiatric disorders also share the same pattern of longitudinal evolution with courses that tend to be chronic and recurrent (Fusar-Poli and others 2019). This chronic nature is currently studied under the neuroprogression framework, defined as the changes associated with the pathological rewiring of the brain that takes place with the progression of severe mental disorders (Berk 2009). Neuroprogression has been associated with loss of gray matter volume, chronic inflammation, changes in growth factors, oxidative stress, and mitochondrial dysfunction across a range of disorders such as bipolar disorder (BD), major depressive disorder (MDD), or schizophrenia (SCZ) (Berk and others 2011b; Davis and others 2014; Moylan and others 2013).

While considering the plasticity of the brain (i.e., the ability of the brain to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections; Cramer and others 2011), it has recently been suggested that it is necessary to emphasize the bidirectional nature of neuroprogression (Moylan and others 2013). Substantial plasticity and remodeling can then be associated with the evolution of psychiatric disorders, and it becomes necessary to revise the current "deficit-oriented" models (Palaniyappan 2017). Indeed, even if neuroplasticity (NP) was initially thought to be limited to critical periods of brain development, it is now largely accepted that NP occurs throughout the lifespan (Pascual-Leone and others 2005). Several famous neuroimaging investigations demonstrate adaptive neuroplastic modifications in the structure (Draganski and others 2004) and function (Amad and others 2017) of the human brain in response to environmental demands in healthy adults and in patients with psychiatric disorders (e.g., Eack and others 2010; Goldapple and others 2004).

In this article, we review evidence that focuses on alteration of the brain associated with the longitudinal evolution of psychiatric disorders from the perspective of *neuroplastic adaptation to pathology*. This new concept highlights that substantial plasticity and remodeling may occur beyond the classic neuroprogressive framework.

Neuroprogression and the Longitudinal Evolution of Psychiatric Disorders

The concept of "neuroprogression" has been proposed to account for changes observed through the natural course of psychiatric disorders (Kapczinski and others 2014). This concept finds its origins in Europe during the mid-19th century, when Jean-Pierre Falret, Karl-Ludwig Kahlbaum, and Joseph Guislain developed the idea of a longitudinal evolution of psychiatric disorders, even until recovery, and emphasized the importance of including longitudinal factors in psychiatric diagnosis. In 1867, Wilhelm Griesinger described these emerging conceptions of neuroprogression as "a constant progressive course, which may proceed even to complete destruction of the mental life" (Griesinger 1867, p. 207). These historical observations of patients presenting with early stages of discrete symptoms that move toward progressive alterations are still relevant with staging models going from very early stages defined by at-risk or latency stages to late or end-stages (Scott and others 2013) (Fig. 1). Neuroprogression has been associated with not only chronic but also recurrent courses. Indeed, psychiatric disorders (e.g., MDD, BD, SCZ, panic disorder [PD], obsessive-compulsive disorder [OCD], anorexia nervosa) show very high relapse rates, and each episode of illness increases the likelihood of future episodes, a phenomenon also known as *kindling* (Post 2007) (Table 1). Similar mechanisms seem to be involved in addictive disorders with significant changes in neural circuitry mediating the motivational system as the disorder progresses, which could drive compulsive drug taking and narrowing the behavioral repertoire to drug seeking (Koob and Moal 2005). BD is probably the disorder that has been the most studied from the perspective of neuroprogression. BD is a recurrent chronic disorder characterized by fluctuations in mood state and energy affecting more than 1% of the world's population (Grande and others 2016). In BD, increased recurrences are associated with a risk of rapid cycling between the depressive and manic states (Berk and others 2011a). This stepwise progression exists not only in clinical symptoms but also in treatment response, neurobiology, and functional impairment (McGorry and others 2010). Berk developed the concept of "pathological rewiring of the brain" to explain the links between clinical evolution of BD and the underlying neuroprogression (Berk 2009). This approach finds its roots in the neurosensitization model proposed by Post and the allostatic load hypothesis by Kapczinski and others (Kapczinski and others 2008; Post 1992). The neurosensitization model postulates that sensitization to both stressors and episodes leads to alterations of neuronal activities that may be transduced at the gene expression level (e.g., the protooncogene c-fos and related transcription factors) (Post 1992). These biochemical and anatomical parameters evolve over time as a function of recurrences and lead to poorer pharmacological responses in affective disorders (Post 1992). The allostatic load hypothesis suggests a direct modulation of brain circuits by stress and episodes leading the patients to become

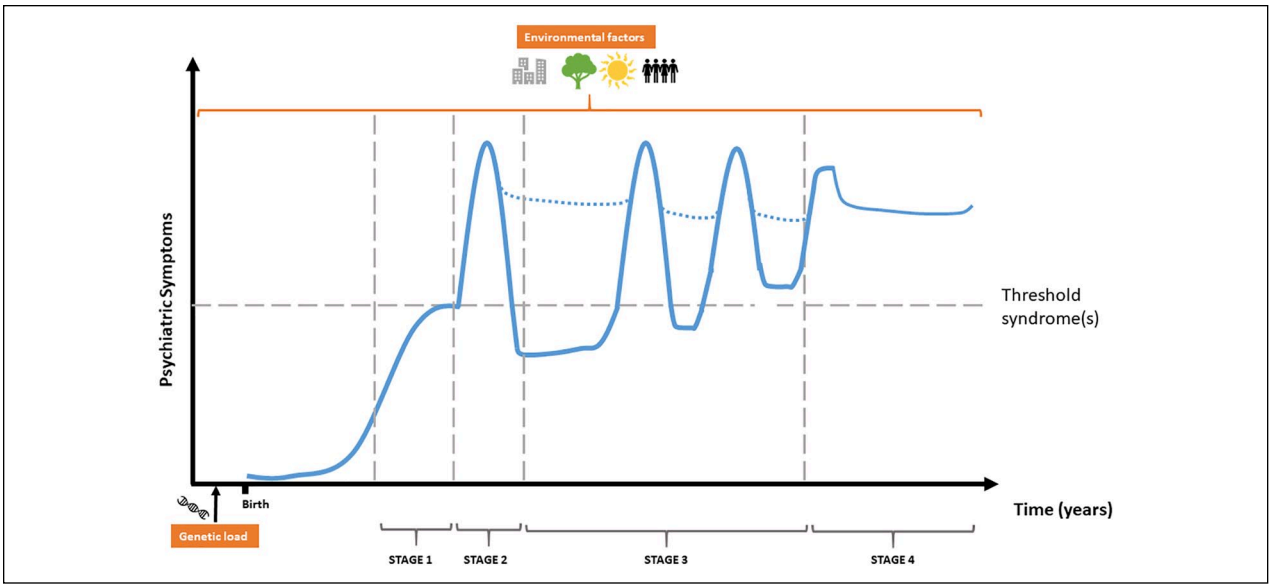

Figure 1. The clinical staging model proposed that major psychiatric disorders develop from an "at-risk" asymptomatic state, through an initial stage of undifferentiated general symptoms (e.g., mild anxiety, sleep disturbance, depressive symptoms) (*stage 1*), followed by a worsening of these existing symptoms and the acquisition of new symptoms, associated with greater syndromal specificity and with behavioral and functional decline. Further progression of illness may then take place, resulting in the occurrence of a first episode of a full-threshold syndrome(s) (*stage 2*), which may be followed by the development of recurrent or persistent symptoms (dotted lines) (*stage 3*) or even severe, treatment-resistant illness (*stage 4*). Interactions, between endogenous (e.g., genes) and exogenous (e.g., drug, urbanicity, social relationships, rhythms) factors, influence the risk of developing a psychiatric disorder as well as the recurrence and persistence of symptomatic episodes.

Table 1. Clinical Characteristics of Psychiatric Disorders or Symptoms from the Perspective of the Repetitiveness and Rates of Recurrence or Relapse.

Disorder	Rate of Relapse and Clinical Aspect of Repetitiveness
Depressive disorder	• Highly recurrent disorder (Moylan and others 2013) • The risk of recurrence after a first major depressive episode is 50% and increases with subsequent episodes (Kendler and others 2000; Post 1992) • Individuals with a history of depression will have five to nine separate episodes in their lifetime (Burcusa and Iacono 2007)
Schizophrenia	• Long-term course of illness is typically characterized by multiple relapses, persistence of symptoms, and enduring cognitive and functional deficits (Andreasen and others 2005) • 60% to 90% of relapses occur within 2 years of a first psychosis episode after treatment reduction/discontinuation (Emsley and others 2013) • 30% have auditory hallucinations that are resistant to treatment (Shergill and others 1998)
Bipolar disorder	• Highly recurrent disorder: 60% relapse 2 years after a major episode (Gitlin and others 1995) • In patients receiving treatment according to contemporary practice guidelines, 58% achieve recovery and 49% develop recurrences over a 2-year period (Perlis and others 2006) • Patients change symptom status (asymptomatic, subthreshold levels, full-blown major depression, and mania) an average of six times per year and polarity (full-blown major depression or mania) more than three times per year (Judd and others 2002)
Panic disorder	• Recurrent panic attacks (Roy-Byrne and others 2006) • Recurrence rate of 25% 2 years after remission (Scholten and others 2013)
Obsessive-compulsive disorder	• Recurrent and persistent thoughts and repetitive behaviors (Abramowitz and others 2009) • 60% relapse 5 years after remission (Eisen and others 2013)

more vulnerable to subsequent environmental stressors, drug abuses, and symptomatic episodes (Kapczinski and others 2008). Numerous biochemical mediators underlying this neuroprogression and stress sensitization have been found to be involved, such as inflammatory processes (including the CRP [C-reactive protein], interleukin [IL]-6, IL-10, and TNF-α [tumor necrosis factor-α]), neurotrophins (including the peripheral blood BDNF), and oxidative stress processes (including the glutathione system; Berk 2009; Munkholm and others 2016).

Neuroprogressive features have also been observed in other psychiatric disorders. MDD is associated with poorer symptomatic, treatment, and functional outcomes in patients with earlier disease onset and an increased number and length of depressive episodes (Table 1) (Moylan and others 2013). Stage-related structural brain changes such as a reduced hippocampal volume are influenced by illness duration, age of onset, and episode frequency in patients with MDD (Eker and Gonul 2010). Moreover, it has been shown that multiple biochemical pathways (inflammation, stress axis, oxidative stress, disturbance to mitochondrial energy production and cell survival mechanisms, and gene transcription alterations) interact simultaneously to cause cellular damage that underwrites the neuroprogression in MDD (Moylan and others 2013).

Schizophrenia is also characterized by neuroprogressive features at clinical and neurobiological levels (Davis and others 2014). Indeed, SCZ has been associated with progressive enlargement of brain ventricles (Van Haren and others 2012) mediated by abnormalities in the cortical gray matter and reductions in white matter surface area (Colibazzi and others 2013; Vita and others 2012). These changes may correlate with symptoms and disorder progression (Vita and others 2012). Like BD and MDD, SCZ has been associated with chronic inflammation, oxidative stress, and mitochondrial dysfunction (Davis and others 2014).

In summary, there is a growing scientific literature observing that multi-scale changes (from behavior to molecular levels) appear during the evolution of psychiatric disorders, from very early "at-risk" phases to different major clinical stages (McGorry and others 2014; Scott and others 2013). These changes may be the consequence of neuroprogression processes that lead to more permanent alterations in late stages. However, it is necessary to consider and emphasize the bidirectional nature of this neuroprogression: substantial plasticity and remodeling can occur (Moylan and others 2013), especially in light of the concept of the economy of the brain.

The Economy of the Brain

The brain is more than an intricate network of neurons connected in an immutable fashion; it is capable of adaptation to its internal and external environment, which endows it with great resilience as a system. Its structure and function continuously change throughout the lifespan of an individual, sometimes drastically due to injury or illness (Bullmore and Sporns 2012). From this perspective, several coherent brain models have been proposed (see, e.g., Friston 2009; Turner 2019). Here we focus on neuroplasticity, which is, as described earlier, arguably one of the key mechanisms that has enabled humans to survive and adapt as a species. In this section, we argue that it is this same capacity for learning and adaptation that may be responsible for the brain's demise in chronic psychiatric disorders.

In this article, we contrast brain evolution and brain adaptation. Brain evolution is the process that has led to general structural and functional organization of the normal brain via genetic mutations and natural selection (Somel and others 2013). Brain adaptation, on the other hand, refers to the changes the brain undergoes post fertilization, either via normal ageing or in response to changes in its environment and integrity such as learning, trauma, or, as we argue here, psychiatric disorders (Amad and others 2017; de Kloet and others 2005).

With the principle of least action guiding the evolutionary process, we can safely assume that the healthy brain is currently the most energy-economic version of the system that yields healthy brain function (Hutto 1999) within an approximately constant energetic budget (Raichle and Gusnard 2002). In the awake state, the available evidence suggests that the adult brain's overall energy consumption is remarkably stable over time. The adult brain continuously consumes large amounts of energy (~20% of the resting total body O_2 consumption) regardless of whether one is engaging in a cognitively or emotionally demanding task or simply resting with their eyes open (Messier 2004; Raichle and Gusnard 2002; Siegel 1999; Sokoloff and others 1955). Most of this baseline energy expenditure is thought to be required for maintaining ion flux related to excitation and conduction (Siegel 1999). Although the neurons activated during a specific cognitive task do require extra blood, oxygen, and glucose, local increases in energy consumption are *very small* compared with the brain's large baseline intake, and are typically accompanied by activity decreases in neighboring areas (Leech and others 2014; Raichle and Gusnard 2002). As a result, it is argued that in the awake state global brain metabolic expenditures are approximately constant and brain dynamics are close to an optimal state, that is, a "sweet spot" (Expert and others 2011), allowing the maximal response range (Kinouchi and Copelli 2006) while reducing energy expenditures incurred by the structural and functional architecture of the brain (Bullmore and Sporns 2012; Chialvo 2010).

The preservation of homeostasis within the brain's energetic budget is paramount to keeping brain dynamics in this operating "sweet spot" and occurs at the global level, with evidence showing that the brain is operating close to an attractive critical point (Expert and others 2011) that allows for a trade-off between segregation and integration. This phenomenon has been proposed as a basis for a model that reconciles multi-level brain function findings in health and in psychiatric disorders such as SCZ (Turkheimer and others 2015). The neurobiological underpinnings of critical brain dynamics are not fully understood, but the available evidence suggests that a complex synergy between the organization of the brain's structural connectome and the excitation-to-inhibition balance in local neuronal populations is likely at play (Froemke 2015; Lord and others 2017; Shew and others 2011). One of the consequences of a system being close to criticality is the similarity of processes at different levels of description. In the case of homeostasis, this similarity is reflected by the synaptic adaptation hypothesis (Tononi and Cirelli 2014), which states that sleep is paramount to regulating synaptic adaption to learning. Synaptic plasticity forms the basis for brain adaptability and our capacity to learn, and these structural changes are also reflected by functional brain changes, which provides a self-similar causality chain from micro- to macroscopic scales (Amad and others 2017; Turkheimer and others 2015).

We propose that certain psychiatric disorders are effectively the result of a brain adaptation mechanism akin to learning. The basis of our argument lies in the brain economy framework, which implies that the brain tries to remain as close as possible to its optimal state (Bullmore and Sporns 2012; Expert and others 2011). We regard the endogenous and/or environmental perturbations linked to the onset of chronic psychiatric disorders as long-term disturbances to normal brain function that are constantly pushing the brain economy away from its optimal healthy state (Roth and others 2009; Rutten and Mill 2009). This phenomenon leads the brain to develop compensatory mechanisms to adapt and preserve the performance of cognitive and behavioral outputs as much as possible and has been associated with the prodromal state of a psychiatric disorder (Lord and others 2011; Lord and others 2012) where, notably, functional connectivity (FC) networks may alter their topology in response to illness to preserve cognitive and behavioral output. However, these resulting new functional pathways may not be optimally supported by the structural connectome and be energetically costly to maintain over time. We therefore hypothesize that these compensatory mechanisms are not sustainable in the long term and that the brain economy becomes overstretched as more energy has to be spent to maintain the most essential regulatory, cognitive, and motor outputs needed for survival (i.e., "baseline" energy expenditure). This compensation therefore increases the baseline energy expenditure and leaves less energy available to carry out more complex cognitive operations that are useful, but not essential for survival (i.e., studying for an exam, planning a trip). This last point is a direct consequence of the maximum energy expenditure of the brain being relatively constant, as outlined above. It is indeed well documented that an increase activity in a brain region has to be matched with either a global or local decrease in energy expenditure (Allison and others 2000; Huang and others 1996; Leech and others 2014; Shmuel and others 2002; Shmuel and others 2006; Tootell and others 1998). In the neuroprogression framework, maintaining homeostasis implies that the brain then has to adapt to the disease and restore brain economy to a less expensive state, given the constraints of the disease and its progression via synaptic plasticity mechanisms akin to learning. This full adaptation means that new structural pathways are created to learn to "cope" with the illness while preserving as much as possible of the brain function and associated cognitive and behavioral outputs. At the same time, it also means that normally used pathways are abandoned over time, which is consistent with numerous imaging studies that find overactivation and underactivation patterns in the brain networks or "connectome" (Crossley and others 2014; Crossley and others 2016), as well as concurrent increases and decreases in FC with conservation of cognitive outputs (Crossley and others 2014; Crossley and others 2016; Lord and others 2011; Lord and others 2012). Once the brain economy is restored with respect to the new functional and structural organization, the brain finds itself in a new "optimal" yet diseased state, and the process is complete. In other words, to preserve its economy, that is, functional dynamics and behavior, the brain learns how to cope with the disease by adapting its structure. The new optimal state requires a higher baseline energy expenditure and therefore has less energy to spend to perform more complex tasks, making it more difficult to maintain cognitive outputs; a recent study shows that the exploration of brain states related to cognitive control of remitted MDD patients is significantly reduced compared with controls (Figueroa and others 2019).

Let us now formalize our proposal illustrated in Figure 2. The simplest model of the brain interacting with its environment consists of a semi-black box that takes inputs and produces outputs. Let us now restrict ourselves to a given set of inputs $\{I\}$. The brain then produces a set of corresponding outputs $\{O\}$, using its anatomical wiring and the function it supports, for a given energetic price E. We denote the set of output expected from a healthy individual and the associated energy as $\{O\}_h$ and E_h, respectively. One way to assess the mental state of a

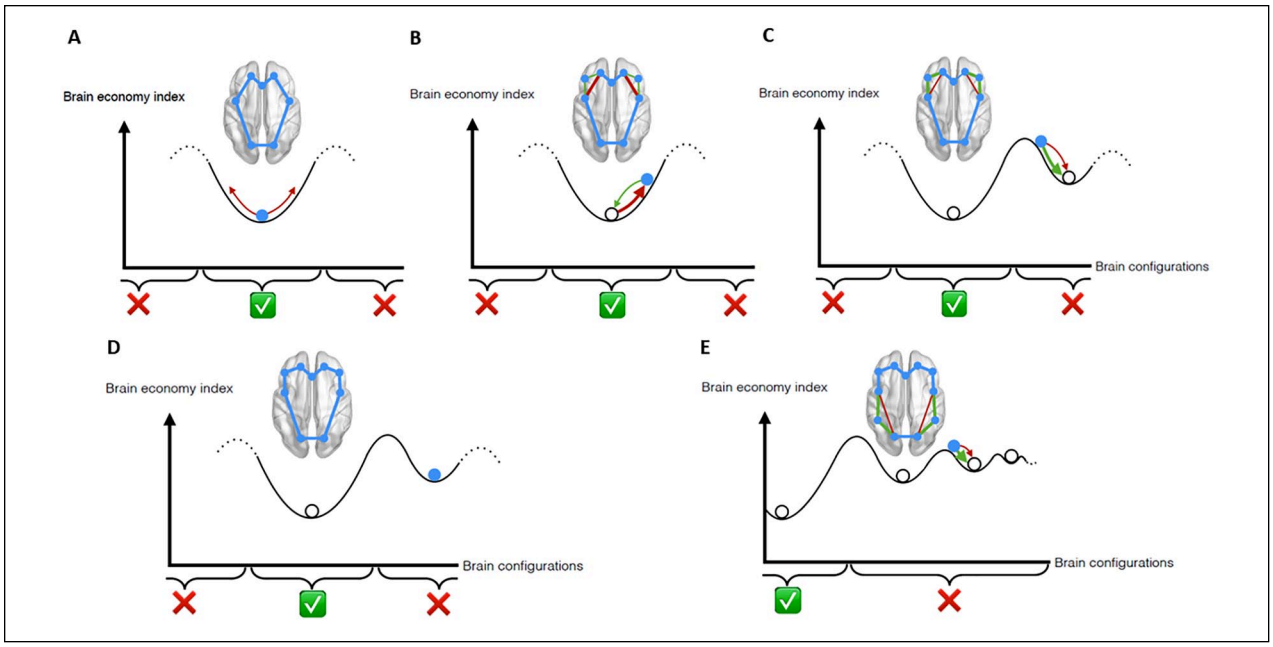

Figure 2. The brain economy paradigm posits that the brain minimizes energy expenditure for a specific functional and structural configuration (FSC). The brain economy index (BEI) then represents a measure of optimality of brain function with respect to energy expenditure and cognitive outputs that is minimized for a healthy FSC. Blue circles: current FSC; Empty circles: locally optimal FSC; Red arrows and links: endogenous and exogenous factors affecting the FSC; Green arrows and links: compensatory mechanisms that try to maintain the FSC into its local optimal. The *x*-axis corresponds to possible FSC, and the *y*-axis corresponds to the associated BEI that takes into account energy expenditure and cognitive outputs of the corresponding FSC. (A) The brain is currently in its optimal healthy FSC condition, and any perturbation would put strain on it. (B) Endogenous and exogenous factors put stress on the FSC and push it away from its optimal point, while compensatory mechanisms try to counter these effects. The compensatory mechanisms cause increased energy expenditure, while perturbating factors cause decreases in cognitive outputs. (C) When the perturbative factors are stronger than the compensatory mechanisms, as in (B), the compensatory mechanisms overstrain the brain FSC and eventually lead to a breakdown (e.g., first psychotic episode) and a reconfiguration and relaxation of the system, dominated by the compensatory mechanisms, into a new FSC that will be locally optimal, that is, lower energy expenditure than during intense straining and suboptimal, but comparatively improved, cognitive outputs. (D) The FSC has settled and adapted to its new local optimum. Being less optimal than the healthy FSC, the new FSC is less stable. (E) Lower barriers, particularly in the direction of worsened symptoms/state, make it more difficult for compensatory mechanisms to contain further endogenous and exogenous perturbations. This phenomenon leads to faster recurrence associated with increasingly worse subject cognitive outputs.

subject is to test his/her answers and/or behavioral responses to a pre-established set of items on the basis of which he/she will be deemed ill, at-risk, or in the healthy range. In our language, this means that if the outputs from a subject deviate more than a given quantity, that individual will be classified as prodromal, diseased, and so on, and we denote such outputs as $\{O\}_d$ and an associated energy expenditure E_d. As reviewed in the next section, functional and structural dysconnectivity have been shown to be present in many psychiatric diseases, and we hypothesize that structural connectivity (SC) and FC indeed deviate from the healthy control baseline in patients (see Fig. 3).

The total energy at the brain disposal is approximately constant and regulated by homeostasis, and our argument posits that, within this energetic budget, compensatory mechanisms will try to preserve the outputs as close as possible to the healthy range in response to exogenous and/or endogenous constraints, doing so by adapting first brain function (FC) and then its structure (SC), at the cost of an increased energy expenditure.

We thus have two quantities that depend on SC and FC, the outputs $\{O\}(SC_i, FC_i)$ and the energy expenditure $E(SC_i, FC_i)$. These values define the brain economy index (BEI), which measures the deviation of the brain economy of a state i from a healthy state by combining the quality of the brain outputs and its energy expenditure as follows:

$$BEI\left(\{O\}_i, E\right) = \alpha\left|\{O\}_h - \{O\}_i\right| + \beta\left|E_h - E_i\right|$$

The constants α and β weight the two contributions and ensure that the BEI is dimensionless. We want to highlight at this point that the present model derived from

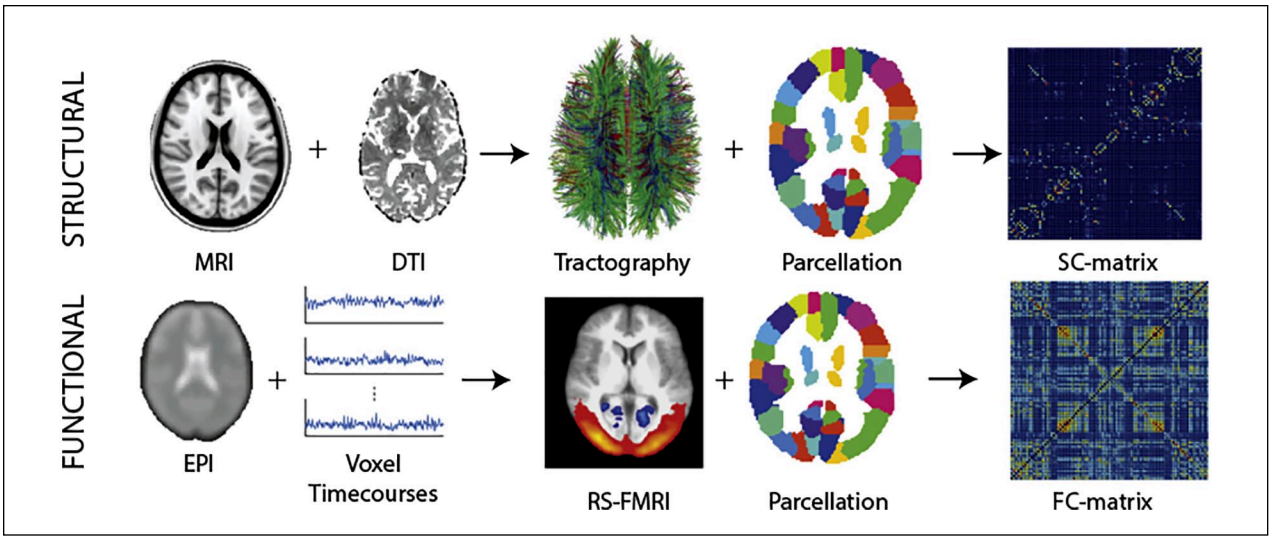

Figure 3. To create a structural connectivity (SC) network, MRI (magnetic resonance imaging) and DTI (diffusion tensor imaging) data are required, on which tractography analysis is then performed to uncover structural links between region pairs. These interactions are summarized in the SC matrix. To create a functional connectivity (FC) matrix, brain activity is measured; in this case using resting-state fMRI to record BOLD time courses in each voxel in the brain. This is then combined with a parcellation scheme to recreate the regional time courses for each of the regions in the chosen parcellation.

the framework introduced here is the simplest formulation that we can justify with the existing literature and aims at being a basis to be enriched as new experimental facts come to light.

We now present Figure 2 to show how the BEI can be used to characterize the evolution and chronicity of psychiatric diseases. In this figure, each minimum corresponds to a combination of FC, SC, and $\{O\}_i$, with the deeper one corresponding to the healthy baseline. Disease-associated exogenous and/or endogenous perturbations will first lead to a modification of FC patterns to maintain $\{O\}_h$, at the cost of an increased energy expenditure, raising the BEI (panel B). When the brain metabolism becomes overstretched, a symptomatic episode occurs, and the system moves into a new basin of $\{O\}_d$. The corresponding outputs are no longer on par with the healthy baseline but allow the energy expenditure to decrease, while reinforcing the changes in FC (panel C) and eventually leading to change in the SC via synaptic plasticity mechanisms, when the system reaches a new minimum of the BEI, as expected from the economy of the brain theory. This new minimum is higher than the healthy baseline because of SC and FC changes and the associated pathological outputs $\{O\}_d$ (panel D). This new minimum is more unstable than the original healthy minimum because its BEI is closer to the level at which disease-related episodes occur. Therefore, the process is more prone to repeating itself, leading to more frequent episodes and disease progression over time (panel E).

Highlighting the Plastic Adaptation to Pathology with Neuroimaging

In this section, we aimed to view brain MRI (magnetic resonance imaging) evidence that can be interpreted from the perspective of the neuroplastic adaptation to pathology.

Structural MRI

Neuroimaging evidence shows both differences in structural features associated with their relevant functions and changes in structural features (gray matter volume and cortical thickness) when long-term neural activity patterns are changed by experience. These changes probably involve many coordinated brain regions that can be explored with the study of changes in the white matter pathway microstructure and the study of white matter connectivity with diffusion tensor imaging (DTI) (Fig. 3). Common measures of DTI include fractional anisotropy (FA), reflecting anatomical white matter features such as axon caliber and myelination. The interpretation of variations in FA is not straightforward; however, a reduced FA is commonly interpreted as a loss in white matter integrity, whereas an increased FA is thought to reflect an increase in white matter connectivity (Dong and others 2004). Many structural neuroimaging studies have thus shown not only a loss of matter in brain volumes among patients suffering from neuropsychiatric disorders; brain volume increases have also been demonstrated in psychiatric disorders such as SCZ, BD, autism, or OCD.

In SCZ, gray and white matter reductions are well documented (Haijma and others 2013). However, the recent study of van Erp and others (van Erp and others 2016) involving more than 2000 patients with SCZ showed that compared with controls, individuals with SCZ exhibited significantly larger pallidum volumes. Interestingly, duration of illness and age were positively associated with pallidum and putamen group contrast effect size. Nonetheless, as highlighted by the authors, these changes may reflect the cumulative effects of antipsychotic medication treatment on basal ganglia volumes reported especially for the putamen (Gur and others 1998; Li and others 2012), even if a disease-related age effect cannot be excluded because larger pallidum volumes in unmedicated, non-ill relatives of individual with SCZ have also been reported (Oertel-Knöchel and others 2012; Yang and others 2012).

In BD, a meta-analysis of gray matter abnormalities using voxel-based morphometry studies revealed that in chronic patients, longer duration of illness was associated with increased gray matter in a cluster that included the basal ganglia, subgenual anterior cingulate cortex, and amygdala (Bora and others 2010).

In OCD, increased gray matter volume has been demonstrated in the basal ganglia (putamen and caudate) (Radua and Mataix-Cols 2009; Radua and others 2010; Rotge and others 2010; Zarei and others 2011), the thalamus (Kim and others 2001), and cortical regions such as left orbital frontal gyrus, right middle frontal gyrus, left middle temporal gyrus, precentral gyrus, and postcentral gyrus (Tang and others 2016). Bilateral cerebellar volume increases and age-related increases in putamen, insula and orbito-frontal cortex volumes have also been reported in a recent mega-analysis (de Wit and others 2014).

In autism, increased gray matter volumes are well known and replicated findings in regions including areas of the temporal and parietal lobes (Yang and others 2016).

Finally, in social anxiety disorder, Talati and others demonstrated that compared with healthy controls, patients exhibited greater gray matter in the left parahippocampal and middle occipital, bilateral supramarginal and angular cortices, and left cerebellum (Talati and others 2013). For other anxiety disorders, Shang and others showed increased gray matter volumes in the right dorsolateral prefrontal cortex in drug-naïve patients with comorbid depression-anxiety (Shang and others 2014).

Functional MRI and Functional Connectivity

Neuropsychiatric disorders are often coined as dysconnectivity syndromes (Buckholtz and Meyer-Lindenberg 2012). The dysconnectivity hypothesis suggests that the existence of impaired connectivity between different brain regions is responsible for abnormal functional integration within neural networks. This impaired connectivity might be associated with an impaired control of synaptic plasticity (Stephan and others 2009). The underlying mechanisms for dysconnectivity remain unknown but likely involve both genetic (Brennand and others 2011) and environmental factors (Sullivan and others 2003), leading to early alterations in the development of brain wiring and impaired experience-dependent synaptic plasticity (Stephan and others 2006). Recently, resting-state FC analyses have been widely used to investigate neuroplastic modifications (Fig. 3). FC corresponds to the temporally correlated, low-frequency spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals across brain regions that occur when a participant is not performing an explicit task (Fox and Raichle 2007). These temporal correlation patterns are not random, and specific networks, such as the default mode network (Greicius and others 2003), have been reliably identified across studies and participants. Moreover, it is now widely accepted that the strength of correlations within and between networks has behavioral relevance (Guerra-Carrillo and others 2014). Interestingly, it has been proposed that FC is an effective measure of plasticity and that activity patterns reflect the history of repeated synchronized activation between brain regions (Guerra-Carrillo and others 2014).

Consistent with the bidirectional nature of the plastic adaptation to pathology outlined above, neuroimaging investigations of FC in psychiatric disorders often reveal not only a loss of FC but also concurrent FC increases in specific neural circuits (Crossley and others 2014; Crossley and others 2016; Lord and others 2011; Lord and others 2012). Importantly, the reported FC increases have been shown in many studies to correlate with the clinical expression of the disease, which suggests that increased FC, as decreased FC, is a pathologically informative feature of brain networks in neuropsychiatric disorders.

In SCZ, a number of studies have found connectivity increases across several brain systems, including the default mode network, cortico-striatal, and thalamocortical pathways (Fornito and Bullmore 2015; Whitfield-Gabrieli and others 2009). Furthermore, in many cases, these FC increases have been positively correlated with symptom severity (Anticevic and others 2014; Fornito and others 2013; Hoffman and others 2011; Whitfield-Gabrieli and others 2009). A recent meta-analysis of 52 seed-based voxel-wise resting-state FC studies showed that SCZ was characterized not only by hypo-connectivity within multiple networks but also by hyper-connectivity between the affective network and the ventral attention network (Dong and others 2018). Interestingly, a brain-wide FC study in 789 participants (343 patients) recently

showed stage-specific functional dysconnectivity across first-episode and chronic stages of SCZ. In first-episode patients, 90% of the functional connectivity changes (from healthy controls) involved the frontal lobes (including Broca's area), whereas for chronic patients, functional connectivity differences extended to wider areas of the brain, including not only reduced thalamo-frontal connectivity but also increased thalamo-temporal and thalamo-sensorimotor connectivity (Li and others 2017).

FC increases have also been reported in mood disorders including BD and MDD. Patients with BD notably show greater connectivity between the amygdala and frontal cortical structures including the anterior cingulate cortex and medial prefrontal cortex compared with healthy subjects (Brady and others 2016; Cerullo and others 2012; Favre and others 2014), which, in turn, has been correlated with the duration of the disease. In MDD, patients show increased FC in the default mode network (Goya-Maldonado and others 2016; Greicius and others 2007), which notably correlates with the number of depressive episodes. Increased fronto-striatal connectivity between the caudate and dorsal prefrontal cortex has also been found in MDD and is positively correlated with the severity of the disorder (Furman and others 2011). Hyper-connectivity between the anterior temporal and subgenual cortices is also a risk marker of subsequent recurring depressive episodes in MDD patients (Lythe and others 2015).

Finally, increased FC has also been found in other disorders such as autism spectrum disorder (ASD) or in anorexia nervosa (AN). Individuals with ASD showed increased FC between primary sensory networks and subcortical networks (thalamus and basal ganglia), and the strength of such connections was associated with the severity of autistic traits in the ASD group (Cerliani and others 2015). Additionally, in AN, increased FC has been observed at rest in the fronto-parietal network, supporting the hypothesis of excessive cognitive control in AN, and of the anterior insula with the default mode network, which may reflect the high levels of self- and body-focused ruminations (Boehm and others 2014).

Neuroimaging evidence in psychiatric disorders such as SCZ, BD, autism, or OCD highlights the plastic adaptation to pathology, with many structural and functional neuroimaging studies observing that there is not only a loss of matter in different brain region volumes or decreased FC but also brain volume increases, along with structural and FC increases or decreases across brain regions. Interestingly, these changes of volume and connectivity are associated with anatomo-clinical correlates, including the disorder progression, the number of episodes of illness, and the duration of disease, highlighting the role of dysconnectivity processes in the adaptation to pathology.

The Neuroplastic Adaptation to Pathology Framework

After having highlighted the high rates of recurrence or relapse in psychiatric disorders from the neuroprogression perspective, the constraints on the brain economy function, and the increases in brain volume and structural and/or FC that may be associated with the clinical features and duration of most major psychiatric disorders, we thus propose to integrate this evidence in the framework of *neuroplastic adaptation to pathology*. Adaptation to pathology can be defined as "the plastic modification of the brain associated with the longitudinal evolution of psychiatric disorders whose courses tend to be recurrent and progressive; with a very high rate of relapse, each episode of illness increases the likelihood of future episodes" (Table 1). Indeed, the brain is essentially a plastic organ, and it is now well known that the repetition of nearly all motor and cognitive skills and processes leads to structural and functional neuroplastic modifications, strengthening those pathways (Amad and others 2017; Draganski and others 2004; Linden 2006). Considering the intensity, duration, and repetition of psychiatric episodes (Bremner 2006; Pol and Kahn 2008), we believe that the brain will also adapt to these episodes. Moreover, the repetition of cognitive or motor skills is known to be executed faster the more they are practiced as a result of neuroplastic changes, until behaviors are executed habitually or automatically in a manner that consumes fewer neural resources, a natural consequence of the brain economy framework (Ashby and others 2010). Based on these observations, we propose a neuroplastic theoretical framework that posits that patients with psychiatric disorders are unfortunate "pathological experts." The repetition of psychiatric episodes and/or symptoms then leads to experience-dependent neuroplastic modifications that increase the likelihood of future episodes and/or symptoms, which ultimately leads to a neuroplastic vicious circle associated with increases in repetitiveness and decreases in behavioral flexibility (Graybiel 2008), regardless of extrinsic environmental triggers.

From the perspective of the plastic adaptation to pathology, the review of neuroimaging studies presented in this article highlights the importance of the basal ganglia and cortical-subcortical connectivity, which appear to be associated with the longitudinal course of psychiatric disorders. The basal ganglia are a set of deep forebrain nuclei consisting of the striatum (caudate and putamen), globus pallidus (internal and external segments), subthalamic nucleus, and substantia nigra (pars reticulata and pars compacta). Interestingly, repetitive behaviors or repetitive cognitive activities are supposed to emerge as a result of experience-dependent plasticity in different basal ganglia-based circuits (Ashby and

others 2010) connected to other brain regions, including the cerebral cortex, thalamus, several brainstem nuclei, and the cerebellum, to form a network with both open- and closed-loop circuitry (Caligiore and others 2017). Thus, although further investigation is required, we believe cortical-subcortical and cerebellum networks related to learning and habits could play a major role in the repetition of episodes of illness involved in psychiatric disorders (Graybiel 2008).

The neuroplastic framework presented here fits well with the dysconnectivity model of psychiatric disorders, which postulates that psychiatric symptoms are associated with impairments in structural and functional brain connectivity in the networks that underpin the functions of everyday human experience (i.e., the cognitive, affective, motor, motivational, and social networks) (Buckholtz and Meyer-Lindenberg 2012). Abnormal connectivity (decreased or increased) between brain areas is associated with impaired control of synaptic plasticity and its underlying mechanisms, which involves both genetic and environmental factors and leads to alterations in brain wiring and impaired experience-dependent synaptic plasticity (Amad and others 2014a; Stephan and others 2006). Thus, rather than the flexible networks with interactions within and between populations of neurons that allow for efficient communication in healthy subjects, patients with psychiatric disorders are characterized by rigid dysconnectivity of the neural networks (Buckholtz and Meyer-Lindenberg 2012). In our framework, the strength of this dysconnectivity is reinforced by the repetition and duration of psychiatric symptoms or episodes (Fig. 2).

Discussion

The framework of adaptation to pathology is a paradigm shift that leads to a novel conceptualization of the pathophysiology of psychiatric disorders and emphasizes the influence of neuroplastic adaptations to symptom repetition that are inherent to the brain's ability to adapt (Pascual-Leone and others 2005). We believe that this framework could make it possible to disentangle the specific pathophysiology of psychiatric symptoms, on the one hand (Buckholtz and Meyer-Lindenberg 2012), and the pathophysiology of the adaptation to pathology, on the other hand (Fig. 2). Fascinatingly, two large-scale systematic meta-analyses of structural MRI and task-fMRI studies across multiple psychiatric diagnoses failed to identify diagnosis-specific effects (Goodkind and others 2015; Sprooten and others 2016). It was then suggested that the abnormalities in brain regions and networks observed in individual MRI studies may reflect brain disorder-general conditions that facilitate the emergence and persistence of symptoms but are insufficient to explain symptomatic variability across disorders (Sprooten and others 2016). The plastic adaptation to pathology also provides a natural framework encompassing the neuroprogression hypothesis. As it has been specifically suggested for schizophrenia, we support the view that progressive changes in psychiatric disorders may not represent a deficit or decompensation process per se but that they could be the result of a distributed, nevertheless inefficient, multi-scale reorganization response (Palaniyappan 2017). Moreover, the concept developed here is a natural consequence of the economy of the brain and fits with the dysconnectivity model of psychiatric disorders. Consideration of the adaptation to pathology framework should aid the integration of the vast and complex translational data across the genomic, neuronal, and behavioral levels. Indeed, it is essential to leverage novel methods for finding patterns and structure in complex, multi-scale datasets from big data and complexity science to develop methodological frameworks to test clinically relevant hypotheses.

The same idea, developed here from a neuroimaging perspective, can then be developed with the genetic approach of psychiatric disorders. Indeed, even if the heritability of psychiatric disorders is important, most genes are shared between disorders, and few genes have been strongly associated with these disorders (Brainstorm Consortium and others 2018). We believe that in one disorder, several genetic pathways interact, involving pathways associated with the development of symptoms and pathways associated with the plastic adaptation to pathology. Thus, vulnerability in the genetic pathway involved in plastic adaptation to pathology may represent risk factors for the repetition of episodes more than the risk for the development of symptoms. Those genes could correspond to plasticity genes modulating the susceptibility to external and internal environment instead of vulnerability genes that would increase the risk of developing symptoms (Amad and others 2014b). The integration of genetic pathways to the framework of the brain adaptation to pathology could help explain the individual variability of vulnerability regarding relapses and chronicity.

Finally, the plastic adaptation to pathology framework should be considered in future fundamental and clinical studies to overcome the scientific and public health challenges posed by psychiatric disorders. To test this framework, scientific methods should not only focus on the differences between patients and disorders but also develop approaches to highlight the factors that are shared within and/or between psychiatric disorders (i.e., a transdiagnostic approach) (Table 2). For example, large brain imaging data sets from patients with different disorders (e.g., schizophrenia, MDD, BD) could be analyzed using methods such as machine learning or pattern recognition to look for connectivity patterns shared by different disorders and associated with the number of episodes or duration of disease. In these studies, multimodal

Table 2. Recommendations for Future Research on the Plastic Adaptation to Pathology.

- Systematically include the duration of illness and the number or relapses in neuroimaging studies
- Focus on chronic and treatment resistant psychiatric disorders
- Development of transdiagnostic longitudinal collaborative studies including genetics and imaging data
- Development of transdiagnostic approaches to highlight the factors that are shared within and between psychiatric disorders
- Development of statistical models for longitudinal data
- Development of statistical methods to highlight what is shared by different groups instead of focusing on differences

Table 3. Summary Table.

- Psychiatric disorders share the same pattern of longitudinal evolution with courses that tend to be chronic and recurrent with a very high rate of relapse, each episode of illness increases the likelihood of future episodes.
- The plastic adaptation to pathology corresponds to the plastic modification of the brain associated with the longitudinal evolution of psychiatric disorders.
- The brain is essentially a plastic organ and all motor and cognitive skills and processes leads to structural and functional neuroplastic modifications.
- The bidirectional nature of neuroprogression needs to be emphasized.
- To maintain homeostasis, the brain then has to adapt to the disease and restore brain economy to a less expensive state, given the constraints of the disease and its progression via synaptic plasticity mechanisms akin to learning.
- This new concept emphasizes the influence of brain adaptations on symptom repetition.
- Patients with psychiatric disorders can be considered as unfortunate "pathological experts."
- The framework of adaptation to pathology could make it possible to disentangle the specific pathophysiology of psychiatric symptoms, on the one hand, and the pathophysiology of the adaptation to pathology, on the other hand.

neuroimaging should be used to quantify the degree of reorganization to grade the severity of the underlying pathophysiological process (Palaniyappan 2017). Additionally, as clinical and functional outcomes are not always stable at an individual level, patients should be assessed at the symptom level across time to provide appropriate variables to study in the plastic adaptation to pathology framework (Palaniyappan 2017). Interestingly, the bidirectional nature of neuroprogression of psychiatric disorders should be tested specifically. Indeed, one of the main alternatives to the framework exposed here could correspond to an absence of homeostasis and to a violation of brain economy principles in patients with psychiatric disorders. In this case, neuroprogression could then be associated with an inexorable energy loss characterized by a lack of neuroplasticity and remodeling in this vulnerable group (See Summary Table 3).

The identification of adaptation to pathology processes in psychiatric patients will be clinically useful, particularly for understanding the high frequency of treatment-resistant psychiatric disorders and explaining why these disorders should be treated as rapidly as possible to prevent self-reinforcement of the pathological network (Sarpal and others 2017; Scott and others 2013). Indeed, this framework suggests that therapeutic interventions should occur as early as possible. At all stages, interventions should aim to prevent relapse and episodes by using course alteration interventions to target the neuroprogression causing a disorder to stop and, ideally, reverse its progression (Millan and others 2016). For each stage, specific interventions should be developed to treat both processes underpinning current symptoms (symptomatic treatment) and the plastic adaptation to pathology (treatment targeting pathological networks). Whereas many symptomatic pharmacological and nonpharmacological treatments are effective in psychiatric disorders, these interventions should be guided by diagnosis for each stage with previously highlighted limits of the traditional psychiatric diagnostic system (McGorry and others 2014). Thus, biomarkers research is expected to be able to disentangle the stages of this common progression of adaptation to pathology in psychiatric disorders. Highlighting the common patterns of psychiatric disorders that are associated with adaptation to pathology would allow us to better target and design treatments by considering them as etiological or symptomatic. Indeed, psychotropic treatments are effective for numerous conditions, for example, the antidepressants used to treat depressive disorder are also efficacious for PD, OCD, and posttraumatic stress disorder, likely because they stop a vicious circle of dysconnectivity reinforcement (i.e., symptomatic treatment) rather than targeting the initial pathophysiology of the disorder (i.e., etiologic treatment). Nonpharmacologic treatments such as cognitive behavioral therapy or physical exercise are also known to enhance brain plasticity and should be considered as add-ons to counteract the plastic adaptation to pathology (Rief and others 2016). Interestingly, the neuroscience of brain

plasticity provides new insights into how to drive "corrective" changes in impaired brains via intensive training that could help hinder and even reverse the adaptation to pathology (Merzenich and others 2014). Finally, circuit-specific interventions targeting pathological networks could be promising strategies (Downar and others 2016), especially when taking the stage associated with the degree of brain reorganization following adaptation to pathology into account.

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