ÉCOLE DOCTORALE BIOLOGIE & SANTÉ UNIVERSITÉ LILLE – NORD DE FRANCE

THÈSE D'UNIVERSITÉ

ÉTUDE DE LA PLASTICITÉ CÉRÉBRALE EN PSYCHIATRIE À PARTIR DE PLUSIEURS MODÈLES PATHOLOGIQUES : LE TROUBLE DE PERSONNALITÉ BORDERLINE ET LES HALLUCINATIONS

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Jury

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RÉSUMÉ

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. Différents troubles psychiatriques peuvent être utilisés 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.

La neuroplasticité individu-dépendante – La NP individu-dépendante permet de concevoir les gènes impliqués dans les troubles psychiatriques comme des gènes de sensibilité à l'environnement plutôt que comme des gènes de vulnérabilité aux maladies. Si l'on considère les gènes de vulnérabilité aux maladies comme des gènes de sensibilité à l'environnement, également appelés gènes de plasticité, les individus qui les portent présentent logiquement une susceptibilité plus grande à l'environnement qu'il soit "négatif" (ex.: maltraitance infantile) ou "positif" (ex.: environnement enrichissant). Ce concept a été proposé dans un modèle intégratif d'un trouble psychiatrique très fréquent : le trouble de personnalité borderline.

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 l'état de stress post-traumatique. Notre hypothèse est que ces deux troubles présentent la même vulnérabilité génétique qui s'exprimera différemment en fonction de l'âge de survenue d'un traumatisme. Nous présentons ici les résultats préliminaires d'une étude génétique d'association, avec réplication interne, d'un gène impliqué dans la régulation de l'axe du stress dans le trouble de personnalité borderline (*FKBP5*).

La neuroplasticité symptôme-dépendante – Cette partie étudie les aspects plastiques de l'hypothèse de la dysconnectivité d'après une approche dimensionnelle permettant de réduire l'hétérogénéité clinique d'une maladie. L'hypothèse de la dysconnectivité 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 plastiques « expérience-dépendants ». 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 cette thèse 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).

Nos résultats, réunis dans cette thèse, mettent en évidence que l'étude des différentes facettes de la NP pourrait permettre une nouvelle compréhension de la physiopathologie des troubles psychiatriques et permettrait d'améliorer les traitements de ces troubles. Il semble en effet que la diversité et l'hétérogénéité des troubles psychiatriques pourrait constituer un avantage sous l'angle de la NP.

INTRODUCTION

Voyageur, le chemin
C'est les traces de tes pas
C'est tout ; voyageur,
il n'y a pas de chemin,
Le chemin se fait en marchant

Antonio Machado

On ne peut pas cueillir une fleur sans déranger une étoile

Proverbe chinois

La **neuroplasticité** (**NP**) correspond à la **capacité du système nerveux à s'adapter, ou à se modifier, aux changements environnementaux internes et externes**. L'utilisation du terme "plasticité" dans le champ des neurosciences est attribuée à Williams James dans son ouvrage *Principles of Psychology* (1890) pour évoquer les voies neuronales modifiées par la répétition. En 1893, Eugenio Tanzi fait l'hypothèse que la plasticité est localisée au niveau des connexions entre neurones, connexions que Charles Scott Sherrington a dénommées "synapse" quelques années plus tard. Au début du XX^{ème} siècle, le grand neuroanatomiste Ramón y Cajal participera également à l'histoire de la NP grâce à ses travaux sur la capacité de régénération et de réorganisation du système nerveux central et périphérique. Les hypothèses concernant les capacités plastiques du cerveau ont été adaptées et développées cinquante ans plus tard par Donald Hebb (1949) qui a énoncé que deux neurones en activité au même moment créent ou renforcent leur connexion permettant une facilitation de la communication entre ces deux neurones. Cette hypothèse a été depuis vérifiée dans les années 1970 par Eric Kandel en étudiant la neurotransmission de l'aplysie (un mollusque marin). Ce dernier a obtenu le prix Nobel de médecine en 2000 pour ces travaux (Berlucchi and Buchtel, 2009).

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 and 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. La maturation comportementale, intellectuelle et émotionnelle de l'enfant est donc étroitement liée à la NP. 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).

Par exemple, l'expérience des jongleurs (Draganski et al., 2004) a montré en utilisant des IRM anatomiques, que des personnes adultes apprenant à jongler présentaient une expansion au niveau de la matière grise des aires cérébrales impliquées dans le traitement des mouvements visuels complexes après 3 mois d'apprentissage. Cette expansion diminuait pour revenir à son état de base quand les sujets arrêtaient de jongler pendant les trois mois suivants. L'étude des chauffeurs de taxis londoniens est un autre célèbre exemple de modification neuroplastique survenant chez des sujets adultes. Cette étude a pu mettre en évidence une augmentation du volume de la partie postérieure de l'hippocampe chez les chauffeurs de taxis par rapport à des contrôles (Maguire et al., 2000).

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 (cf. **Figure 1**) (Kolb and Gibb, 2011).

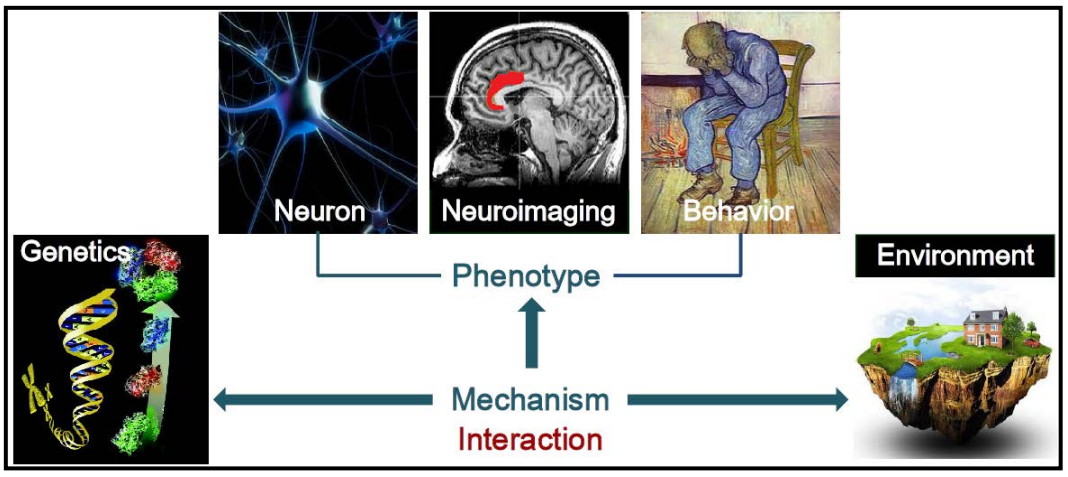

Figure 1: approche translationnelle et multimodale des troubles psychiatriques. (D'après (Ge et al., 2013)).

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. 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).

Les troubles psychiatriques regroupent des entités très hétérogènes dont les différences sont marquées au niveau physiopathologique, étiologique, et bien entendu clinique. Différents troubles psychiatriques peuvent ainsi 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 thèse, différentes facettes de la NP seront explorées en utilisant des modèles physiopathologiques distincts permettant une nouvelle lecture de la physiopathologie des troubles psychiatriques (Cf. **Tableau 1**). L'utilisation et l'optimisation de thérapeutiques centrées sur la NP, notamment les méthodes de neuromodulation, seront également abordées.

Facette de la neuroplasticité testée	Caractéristique	Modèle pathologique utilisé
Neuroplasticité individu-dépendante	Les individus présentent des sensibilités à l'environnement différentes sous-tendues par des gènes de sensibilité à l'environnement (appelés gènes de plasticité) différents.	Interaction gène-environnement dans le trouble de personnalité borderline d'après le concept des gènes de plasticité.
Neuroplasticité âge-dépendante	La NP, régulée différemment selon les périodes de développement, entraine des conséquences comportementales différentes selon l'âge de survenue d'un évènement ou d'une expérience.	Génétique du trouble de personnalité borderline centrée sur les gènes impliqués dans la régulation de l'axe du stress.
Neuroplasticité symptôme-dépendante	Approche neuroplastique centrée sur une dimension clinique plutôt que sur un trouble entier.	Étude de la dysconnectivité dans les hallucinations.

Tableau 1 : Les différentes facettes de la neuroplasticité explorées dans cette thèse.

LA NEUROPLASTICITÉ INDIVIDU-DÉPENDANTE

Le microbe n'est rien. Le terrain n'est rien. L'interaction est tout.

2.1. Les gènes de sensibilité à l'environnement ou gènes de plasticité

Chez des individus exposés au même environnement, il existe des différences importantes de réponse à ce même environnement. Ces différences sont associées à des susceptibilités génétiques différentes entre les individus. La NP individu-dépendante permet alors de concevoir les gènes impliqués dans les troubles psychiatriques comme des gènes de sensibilité à l'environnement plutôt que comme des gènes de vulnérabilité aux maladies (Caspi et al., 2010). Ainsi, tous les sujets n'ont pas la même sensibilité à l'environnement.

L'exemple du gène du transporteur de la sérotonine (*5-HTT*) est particulièrement évocateur de cette problématique. Le *5-HTT* régule la concentration de sérotonine disponible dans la synapse en recaptant la sérotonine libre. Un polymorphisme fonctionnel de la région promotrice du gène a été identifié (*5HTTLPR*) et permet de distinguer l'allèle court (S) associé à une réduction de la transmission sérotoninergique et l'allèle long (L) associé à une transmission sérotoninergique plus importante. L'allèle de faible expression du *5-HTTLPR* (S) est considéré comme un facteur de risque génétique pour le développement de troubles psychiatriques, notamment les troubles de l'humeur et anxieux, en lien avec une majoration de la sensibilité à l'environnement (Caspi et al., 2010) (cf. **Figure 2**).

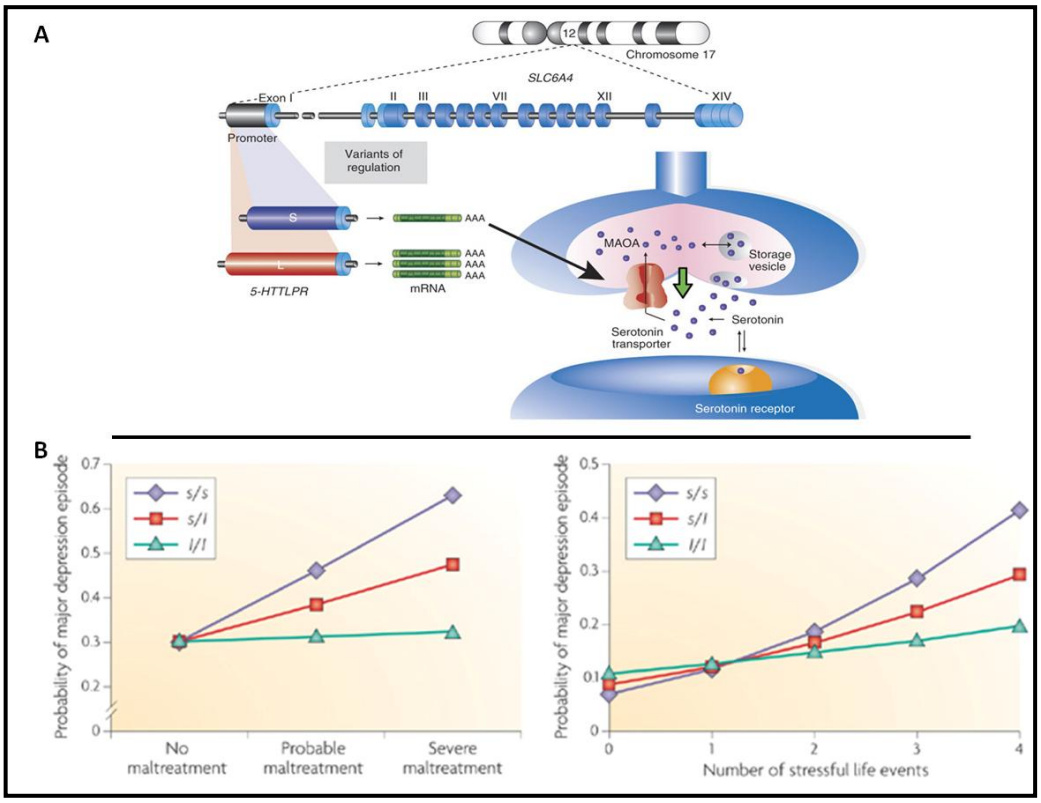

Figure 2 : Approche classique de l'interaction gène-environnement en psychiatrie. **A)** Le transporteur de la sérotonine présente un polymorphisme fonctionnel de la région promotrice du gène et permet de distinguer l'allèle court (S) et l'allèle long (L). **B)** L'allèle S est considéré comme un facteur de risque génétique pour le développement de troubles psychiatriques, ici la dépression, quand il interagit avec des facteurs de risque environnementaux, ici la maltraitance infantile. D'après (Burmeister et al., 2008; Canli and Lesch, 2007).

Si l'on considère le *5-HTT*, non pas comme un gène de vulnérabilité aux maladies mais comme un gène de sensibilité à l'environnement, également appelés **gène de plasticité**, les individus présentent logiquement une susceptibilité plus grande à l'environnement quel qu'il soit, c'est-à-dire qu'il soit "négatif" (ex. : maltraitance infantile) ou "positif" (ex. : environnement enrichissant et stimulant) (Belsky et al., 2009). En effet, il faut rappeler que tous les individus porteurs de l'allèle S, considérés comme vulnérables aux troubles anxieux et à la dépression, notamment quand ils ont été exposés à des évènements de vie difficiles, d'une part ne souffrent pas de troubles psychiatriques ou de dérégulation émotionnelle. D'autre part, ces sujets présentent de meilleures performances que les sujets porteurs de l'allèle L à des tâches cognitives (prise de décision, tâche attentionnelle), artistiques (création de chorégraphie de danse), ainsi qu'à des tâches permettant de mesurer certaines aptitudes sociales (conformité sociale) (Homberg and Lesch, 2011).

Considérer le transporteur de la sérotonine comme un gène de plasticité plutôt qu'un gène de vulnérabilité permet d'imaginer que selon les facteurs environnementaux la réponse comportementale d'un individu sera négative (ex: dérégulation émotionnelle) ou positive (ex : créative ou cognitive), les gènes de plasticité étant associés à une sensibilité augmentée à l'environnement "pour le meilleur et pour le pire". Dans l'**Article 1**, le concept de "gènes de plasticité" a été appliqué en utilisant le Trouble de Personnalité Borderline (TPB) comme modèle.

2.2. Application du concept de gènes de plasticité au trouble de personnalité borderline

2.2.1. Perspective historique

Le terme borderline est introduit pour la première fois dans le champ analytique dans un souci de distinguer les patients névrotiques et psychotiques. Il est utilisé par Stern (Stern, 1938) dans un premier temps puis par Knight (Knight, 1953) pour décrire certains patients névrotiques qui développent au cours de la cure analytique un transfert d'ordre psychotique décrit comme une schizophrénie borderline ("état mental astructuré").

Une contribution majeure sera apportée dans les années soixante à ce concept grâce aux travaux d'Otto Kernberg qui définira la structure de personnalité borderline comme une organisation de personnalité limite entre névrose et psychose, marquée par le clivage et l'identification projective. Il met également pour la première fois en évidence l'importance de la problématique abandonnique et les carences infantiles majeures chez ces patients (Kernberg, 1967). C'est également dans les années 70 qu'en France, Bergeret développe une théorie générale de la structuration limite de la personnalité considérée là encore comme un intermédiaire entre névrose et psychose. Il décrit différentes formes cliniques plus ou moins proches de la névrose ou de la psychose (Bergeret et al., 2004).

A partir de ces descriptions de l'organisation de la personnalité borderline, les travaux de Grinker ont pour but de définir des critères diagnostics valides, évaluables et permettant la distinction avec d'autres troubles mentaux (Grinker et al., 1968). Ce sont ces travaux qui vont inscrire le TPB dans le DSM III. La définition du TPB est, à cette époque, encore floue et même si la séparation avec la schizophrénie est de plus en plus nette, son entité est encore discutée. Elle est par exemple pour Akiskal une forme atypique de trouble de l'humeur (Akiskal, 1981).

Le développement de critères diagnostics et des méthodes issues de la psychiatrie biologique permettent par la suite de montrer que le diagnostic TPB a une consistance interne, avec une évolution de la maladie propre, différente de la schizophrénie et des troubles de l'humeur. Il est également montré que ce trouble présente une agrégation familiale (Loranger et al., 1982), que la prévalence de la schizophrénie n'est pas augmentée dans les familles de patient souffrant de TPB, et même que des médications pharmacologiques peuvent améliorer certaines dimensions symptomatologiques de façon modérée (Pope et al., 1983).

Par la suite, les considérations étiologiques se développent et, même si cela était connu de façon empirique, la grande prévalence (70 %) de maltraitance infantile chez les patients souffrant de TPB est démontrée (Herman et al., 1989). Torgersen en 2000 confirme l'agrégation familiale du trouble ainsi que la participation génétique au TPB avec une étude de jumeaux. Il retrouve une héritabilité (poids des facteurs génétiques) à 70 % pour le TPB (Torgersen et al., 2000).

La recherche concernant la prise en charge des patients souffrant de TPB s'est également considérablement développée, au niveau psychothérapeutique avec la thérapie dialectique de Linehan (Linehan, 1987) ainsi qu'au niveau pharmacologique, ce qui donne même lieu à l'heure actuelle à des méta-analyses comparant l'efficacité de différentes molécules dans la prise en charge du TPB (Lieb et al., 2010). Ces développements méthodologiques, ont permis de mettre en place plusieurs études de suivi qui montrent toutes une diminution de l'impulsivité avec l'âge (Amad et al., 2013). Enfin pour certains auteurs, la meilleure connaissance de la maladie, son évolution, ainsi que les développements thérapeutiques de plus en plus spécifiques font du TPB, une maladie de bon pronostic (Gunderson, 2009).

2.2.2. Présentation clinique

Le TPB est le plus fréquent des troubles de la personnalité. Il touche en effet 0,5 à 6 % de la population générale (Leichsenring et al., 2011), et malgré une idée répandue, on ne retrouve pas, en population générale, de différence de prévalence entre les hommes et les femmes (De Moor et al., 2009; Lenzenweger, 2008). Il représente environ 10 % des patients suivis en ambulatoire et 10 à 20% des patients hospitalisés en psychiatrie (Skodol et al., 2002).

La clinique du TPB est marquée par des troubles affectifs (instabilité émotionnelle, sentiment envahissant de vide), des distorsions cognitives (expériences dissociatives, jusqu'à d'authentiques symptômes psychotiques), des troubles du comportement liés à l'impulsivité (auto-mutilation et tentatives de suicide répétées) et une instabilité interpersonnelle majeure (relations intenses et instables) (Lieb et al., 2004). Le diagnostic de TPB est classiquement posé chez des adultes jeunes, et la symptomatologie tend à s'amenuiser avec l'âge comme le montrent plusieurs études de suivi (Amad et al., 2013). On distingue alors des symptômes aigus (impulsivité, auto-mutilation, comportement suicidaire, éléments psychotiques liés au stress) dont la rémission est rapide et des symptômes chroniques (dysphorie, intolérance à la solitude, vécu abandonnique, difficultés dans les relations interpersonnelles) (Zanarini et al., 2007).

Une des principales complications évolutives psychiatriques du TPB est le comportement suicidaire, avec une mortalité très importante (environ 10%). On retrouve également de nombreuses comorbidités telles que les troubles de l'humeur (dépression, trouble bipolaire, dysthymie), les conduites addictives et les troubles du comportement alimentaire (Skodol et al., 2002). Les patients souffrant de cette pathologie ont également tendance à la surconsommation de médicaments et nécessitent souvent de nombreuses hospitalisations.

2.2.3. Une étiologie complexe

L'étiopathogénie du TPB est complexe. En effet, à partir des années 90, plusieurs études ont démontré la grande fréquence d'antécédents traumatiques (maltraitance, négligence, abus sexuels, séparation précoce) chez les patients souffrant de TPB. Selon les études, on retrouve des antécédents de maltraitance infantile, notamment d'abus sexuel, dans 40 à 90 % des cas. Ces antécédents sont plus fréquents, plus précoces et plus sévères que chez les patients présentant d'autres troubles de personnalité. Cependant, aucun de ces antécédents n'est considéré comme spécifique du TPB et aucune association assez forte n'a pu être montrée entre ces antécédents de maltraitance et le développement d'un TPB (Leichsenring et al., 2011). De façon intéressante, une vulnérabilité génétique a été identifiée chez les patients souffrant de TPB (Skodol et al., 2002). L'**Article 1** est une revue systématique de la littérature sur la génétique du TPB. Dans cet article une méta-analyse des études d'association a été réalisée ainsi qu'une proposition de modèle intégrant le concept de gène de plasticité.

ARTICLE 1

Genetics of borderline personality disorder:

Systematic review and proposal of an integrative model

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Genetics of borderline personality disorder: Systematic review and proposal of an integrative model

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ABSTRACT

Borderline personality disorder (BPD) is one of the most common mental disorders and is characterized by a pervasive pattern of emotional lability, impulsivity, interpersonal difficulties, identity disturbances, and disturbed cognition. Here, we performed a systematic review of the literature concerning the genetics of BPD, including familial and twin studies, association studies, and gene–environment interaction studies. Moreover, meta-analyses were performed when at least two case-control studies testing the same polymorphism were available. For each gene variant, a pooled odds ratio (OR) was calculated using fixed or random effects models. Familial and twin studies largely support the potential role of a genetic vulnerability at the root of BPD, with an estimated heritability of approximately 40%. Moreover, there is evidence for both gene–environment interactions and correlations. However, association studies for BPD are sparse, making it difficult to draw clear conclusions. According to our meta-analysis, no significant associations were found for the serotonin transporter gene, the tryptophan hydroxylase 1 gene, or the serotonin 1B receptor gene. We hypothesize that such a discrepancy (negative association studies but high heritability of the disorder) could be understandable through a paradigm shift, in which "plasticity" genes (rather than "vulnerability" genes) would be involved. Such a framework postulates a balance between positive and negative events, which interact with plasticity genes in the genesis of BPD.

Keywords: borderline personality disorder, genetics, gene–environment interaction, plasticity genes

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., 2004b). BPD is estimated to occur in 0.5–5.9% of the general population (Grant et al., 2008; Lenzenweger et al., 2007) and is the most common personality disorder in clinical settings, affecting 10% of all psychiatric outpatients and 15%–20% of inpatients (Skodol et al., 2002a). The disorder is equally prevalent among men and women (De Moor et al., 2009; Grant et al., 2008) 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). However, 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., 2002a; Tomko et al., 2013). Lastly, BPD is associated with high mortality due to suicide (up to 10% of patients commit suicide), frequent hospitalization, substance use, and poor quality of interpersonal relationships (Skodol et al., 2002a).

The etiology of borderline personality disorder is complex. Patients with BPD report many negative events during childhood, such as neglect (92%), sexual abuse (40%-70%), physical abuse (25%-73%) (Zanarini et al., 2002, 1997), parental divorce or illness (Paris et al., 1994), and parental psychopathology (Trull, 2001). Moreover, these patients report more adverse events than patients with other personality disorders (Yen et al., 2002). Childhood adversity accounts for one of the largest proportions of variance explained (27.8%) compared to the nine other personality disorder dimensions (Hengartner et al., 2013). However, none of these antecedents is considered specific to BPD (Hengartner et al., 2013; Paris and Zweig-Frank, 1992; Paris, 2007). Moreover, the strength of these associations might be relatively weak. For example, in a meta-analysis, Fossati and collaborators found that the effect size of the association between BPD and childhood sexual abuse was low, with a correlation (r) equal to 0.28 (Fossati et al., 1999). New et al. argued that the belief that BPD may be the direct consequence of early trauma is a misconception (New et al., 2008). For example, 80% of subjects with a history of sexual abuse do not fulfill the criteria for a personality disorder (Paris, 1998). A longitudinal follow-up of abused children showed a high rate of resilience

(McGloin and Widom, 2001), and in an outpatient sample of well-characterized personality disorder subjects, childhood physical and sexual abuse did not appear to predict BPD (Bierer et al., 2003).

Interestingly, a genetic vulnerability has been identified in patients with BPD (Skodol et al., 2002b), and the recent interest in the potential interaction between genetic and psychosocial factors (e.g., childhood abuse) in BPD (Gabbard, 2005; Leichsenring et al., 2011; Lieb et al., 2004b; Paris, 1998) might help to more adequately identify the involved risk factors and determine their actions and interactions if the heritability of BPD is significant enough to be integrated into complex models. We therefore examined the existing literature on the genetics of BPD, and meta-analyses were performed when two or more case-control studies testing the same polymorphism were available. To our knowledge, this is the first review to systematically summarize all of the available literature on the genetics of BPD and to propose an integrative model in line with the results of a meta-analysis of association studies.

2. METHODS

2.1. Literature search strategy

To identify studies eligible for this review, a systematic search was conducted using the Medline and Scopus databases up to October 2013 using the following search term combinations: "borderline personality disorder", "gene", "genetic", "genetics", "polymorphism", and "haplotype". We also examined the reference sections from the selected papers to identify any additional relevant studies. Papers were included in the systematic review if (a) they were published in an English-language peer-reviewed journal; (b) the study enrolled patients with BPD or subjects with borderline personality traits (BPT); (c) the diagnosis was made according to the Diagnostic and Statistical Manual (DSM) criteria; and (d) patients or subjects were at least eighteen years old. Article titles and the abstracts of studies identified from the searches were screened and excluded from the systematic review for the following reasons: not written in English; not genetic research; review article, opinion, or hypothesis article; and samples with a disorder other than BPD. The full text of studies that passed the initial screening was reviewed and potentially excluded based on the same criteria. We clustered the retained papers into familial aggregation studies, twin studies, association studies, and gene-environment interaction (G x E) studies. With respect to the PRISMA statement (Moher et al., 2009), the literature search strategy is summarized in the flow chart presented **Figure 1**.

INSERT FIGURE 1 ABOUT HERE

2.2. Statistical analyses

Meta-analyses were performed if two or more case-control studies testing the same polymorphism were available. The odds ratio (OR) and its 95% confidence interval (CI) were estimated for each study. Heterogeneity was tested with the Cochran *Q* test. For each gene variant, a pooled odds ratio (OR) was calculated using fixed-effects (Mantel-Haenszel method) and random-effects models (DerSimonian and Laird method). Statistical analyses were performed with MIX 2.0 statistical software (Bax et al., 2007).

3. RESULTS

3.1. FAMILIAL AGGREGATION STUDIES

The hypothesis of genetic involvement in BPD arose from family studies showing the existence of a familial aggregation. These studies analyzed the frequency of BPD in first-degree relatives of a subject with BPD compared with the general population or first-degree relatives of healthy subjects. In these studies, probands and relatives were assessed by chart reviews (Loranger et al., 1982; Pope et al., 1983), self-reporting (Reich, 1989), and structured interviews (Bandelow et al., 2005; Baron et al., 1985; Johnson et al., 1995; Links et al., 1988; Riso et al., 2000; Stone et al., 1981; Zanarini et al., 2004, 1988). With the exception of the study by Pope et al. in 1983, which showed a risk of BPD in relative probands of 0.8, all other studies show risks ranging from 5.1 (Baron et al., 1985) to 22.2 (Riso et al., 2000). Recently, the presence of familial aggregation was confirmed (Gunderson et al., 2011) because the risk of a BPD diagnosis, as assessed by a structured interview (Diagnosis Interview for Borderlines (DIB-R)), in the relatives of a proband with BPD (prevalence of 14.1%) was 3.9 times higher than the risk of diagnosis in the relatives of a proband without BPD (prevalence of 4.9%, $p<.001$). Such familial aggregation was also shown for the four main dimensions of BPD (emotional lability, impulsivity, interpersonal difficulties, and disturbed cognition), leading the author to conclude that familial factors contribute to BPD and its sectors of psychopathology (Gunderson et al., 2011).

Family studies only suggest the role of genetic factors; they do not distinguish between genetic and shared environmental factors. For this purpose, twin studies are usually performed.

3.2. TWIN STUDIES AND HERITABILITY

Twin studies are useful for distinguishing the impact of genetic and environmental factors. To specifically estimate the percentage of the phenotypic variance explained by genetic factors, twin studies explore the difference in concordance rates between monozygotic and dizygotic twins (Boomsma et al., 2002). Furthermore, environmental influences can be divided into shared environment, corresponding to an environment shared by family members, and non-shared (or unique) environment, corresponding to environmental influences that are unique to each individual (van Dongen et al., 2012).

Twin studies have been used to estimate the heritability of BPD. Heritability, defined as the

proportion of observed variation that can be attributed to inherited genetic factors rather than environmental factors, can be estimated from the difference in the correlation between monozygotic (MZ) and dizygotic (DZ) twins ($h^2=2(r_{MZ}-r_{DZ})$). The first twin study on BPD reported a MZ concordance rate of 0% and a DZ concordance rate of 11.1% for BPD (Torgersen, 1984). However, this study included a small number of twin pairs (n = 25), thereby limiting any conclusions. Since this first publication, several other twin studies have been performed with larger samples, and the mean heritability has been estimated to be approximately 40%. Torgersen et al. assessed 221 twin pairs using the structured clinical interview for DSM-III-R (SCID-II) and showed a heritability of 69% for BPD. However, this study had several limitations; notably, the sample was recruited from patient populations, and the same interviewers often interviewed both the proband and the cotwin (Torgersen et al., 2000). More recently, two studies on 2794 and 1386 twins from the general population assessed by the Structured Interview for DSM-IV Personality Disorder (SIDP-IV) showed heritabilities of 37.1% (Kendler et al., 2008) and 35% (Torgersen et al., 2008), respectively. In a study on 2801 Young adult twins from the population-based Norwegian Institute of Public Health Twin Panel, the heritability of BPT, assessed with the SIDP-IV, was estimated around 35% (Reichborn-Kjennerud et al., 2010). Moreover, this study showed that vulnerability to BPT and MDD was closely related, including both genetic and environmental factors. Another multivariate twin study on 2794 young twins assessed by the SIDP-IV found that one highly heritable factor (heritability of 55%) influences all 9 BPD criteria, whereas environmental factors influence only affective and interpersonal dimensions (Reichborn-Kjennerud et al., 2013). These results are consistent with those obtained when self-reporting (Personality Assessment Inventory for BPD (PAI-BOR)) was used to assess 5496 twins (1852 complete pairs) from The Netherlands, Belgium, and Australia. The results of this study showed a consistent heritability of 42% across the three samples (Distel et al., 2008b). Recently, the heritability of BPD (assessed by both a self-report questionnaire and the SIDP-IV) in 2800 twins from Norway was estimated as being closer to 67% (Torgersen et al., 2012).

In a longitudinal twin study, Bornovalova and colleagues examined the course and heritability of BPD, which was assessed by a self-report (Multidimensional Personality Questionnaire), over a period of ten years, from adolescence to adulthood. These authors showed that BPD traits were moderately heritable at all ages, with a trend toward increased heritability from age 14 to 24. Moreover, the results showed that the stability of BPD traits was highly influenced by genetic factors and was modestly influenced by non-shared environmental factors (Bornovalova et al., 2009).

Lastly, Distel and colleagues performed the only twin study including molecular genetic analysis through a genome-wide linkage of 711 sibling pairs (300 dizygotic male twins and brothers and 510

dizygotic female twins and sisters) and 561 additional parents. These authors found that chromosome 9p22 was the region with the highest logarithm of odds (LOD) score (3.548), signifying that this genomic region has the highest likelihood of being co-transmitted with the studied phenotype (here, BPD) (Distel et al., 2008a).

3.3. EXTENDED TWIN STUDIES

The design of twin studies can be extended to include parents, siblings, spouses, and offspring of MZ and DZ twins to study the cultural transmission, G x E, and gene–environment correlation (Boomsma et al., 2002). Indeed, according to Kendler and Eaves, three models can influence the vulnerability to psychiatric disease: additive effects of genotype and environment, genetic influence on sensitivity to the environment (G x E), and genetic influence on exposure to the environment (gene–environment correlation) (Kendler and Eaves, 1986). An extended twin studies design using a genetic models approach has thus been utilized to study borderline personality traits (BPT). Indeed, in all studies that include several thousands of subjects, borderline features were assessed using self-reporting, and BPT is thus more appropriate than BPD.

Distel and colleagues have performed several extended twin studies based on a large twin cohort. In addition to MZ and DZ twins, these authors collected data from siblings, spouses, and parents of twins. These studies showed that, for BPT, the resemblance among biological relatives could be completely attributed to genetic effects, and cultural transmission from parents to offspring did not have an effect. Furthermore, variation in BPT was explained by genetic and environmental factors (Distel et al., 2009a). Interestingly, this type of analysis, which was performed on 5083 twins and 1285 non-twin siblings assessed for traumatic life events, provides evidence for both G x E and gene–environment correlation, indicating the importance of genetic factors and life events in the genesis of BPT (Distel et al., 2010). Moreover, genetic and environmental effects have been shown to influence the four main dimensions of BPT (Distel et al., 2010).

Extended twin studies design was also applied to the dimensional approach to BPD. The dimensional approach of personality conceptualizes personality disorders as extreme and maladaptive variants of normal personality traits that are continuously distributed in populations and are assessed by quantitative evaluation (Skodol, 2005). One of these models corresponds to the Five-Factor Model (FFM) of personality traits, which subdivides personality into five main domains (i.e., neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) (Costa and MacCrae, 1992). Interestingly, in a web-based sample of 44 112 subjects, including 542 twin

pairs, assessed by the Dimensional Assessment of Personality Pathology Basic Questionnaire and Big Five Inventory, a complex pattern of genetic and environmental associations was found in the dimensions of BPT defined on the basis of the Big Five personality traits (Kendler et al., 2011). Participants in this study were part of the survey entitled, "Twins: an interactive personality test", in which 609 twins, 342 dating partners, 313 'significant other' pairs, 327 spouses, and 2316 friend pairs were included (Kendler et al., 2009). Distel et al. showed that a combination of high neuroticism and low agreeableness best predicted borderline personality, and the strongest genetic correlations with BPT were observed for neuroticism (positive), followed by conscientiousness (negative) and agreeableness (negative) (Distel et al., 2009b).

Several twin studies were performed by Distel and colleagues to examine psychiatric comorbidities in BPT. These studies showed a phenotypic correlation of 0.59 between BPT and attention-deficit/hyperactivity disorder (ADHD) symptoms; this correlation was explained by 49% genetic factors and 51% environmental factors (Distel et al., 2011). Similarly, these authors found a significant phenotypic correlation between anger and BPT (r = 0.52). This correlation was explained by genetic influences for 54% of the global variance and by unique environmental influences for 46% of the global variance (Distel et al., 2012a). Lastly, the same team recently observed significant associations between BPT and a high level of alcohol consumption (r = 0.192, 95% CI [0.116 – 0.269]), regular smoking (r = 0.299, 95% CI [0.250 –0.348]), and ever using cannabis (r = 0.254, 95% CI [0.195 – 0.313]) (Distel et al., 2012b). Different etiologies have been determined for such comorbidities. Bivariate genetic analyses showed that the association between a high level of alcohol consumption and BPT was explained by unique environmental factors, whereas the correlation between BPT, regular smoking and ever using cannabis was explained by common genetic factors (Distel et al., 2012b).

3.4. ASSOCIATION STUDIES ON BPD

Association studies identify genetic variants that influence the risk of BPD. In genetic case-control studies, the frequency of alleles (or genotypes) is compared between cases and controls. **Table 1** summarizes association studies performed on BPD and indicates which studies were used for the present meta-analyses.

INSERT TABLE 1 ABOUT HERE

3.4.1. The Serotonin System

Tryptophan Hydroxylase Gene

Serotonin (5-hydroxytryptamine (5-HT)) is a neurotransmitter that has been implicated in a wide variety of neurobehavioral processes, including cognition, affective states, impulsivity, and ingestive behavior. 5-HT is synthesized in two steps from the amino acid tryptophan, with tryptophan hydroxylase (TPH) as the rate-limiting enzyme. Tryptophan hydroxylase-1 (TPH1) is responsible for the synthesis of peripheral 5-HT, whereas tryptophan hydroxylase-2 (TPH2) is neuron-specific and controls central 5-HT synthesis (Savelieva et al., 2008).

In a case-control design study, Zaboli et al. compared 98 women without a psychiatric history and 95 suicidal patients with a BPD diagnosis (Zaboli et al., 2006). Six single-nucleotide polymorphisms (SNPs) in the *TPH1* gene were screened. None of the SNPs was individually associated with BPD; however, several haplotypes were identified in excess in the BPD group. A six-SNP haplotype ("ACGCCG") was absent from the control group and constituted approximately one-quarter of all haplotypes in the BPD group (corrected $p < 10^{-5}$). Most of the significant associations encompassed the region of the gene between the promoter and intron 3. The authors concluded that the *TPH1* gene was associated with BPD in suicidal women (Zaboli et al., 2006).

Following this work, the same team used the Iowa Gambling Task (IGT) to examine social decision-making in women with BPD and explore the relationship between impaired decision-making and the *TPH1* gene. A total of 42 women with BPD and a history of suicide attempts were genotyped along with 30 controls, and the frequency of the ACGCCG haplotype was calculated. The BPD group scored significantly lower on the IGT than the control group, corresponding to impaired decision-making. Moreover, the frequency of the *TPH1* ACGCCG haplotype was significantly higher in BPD participants with impaired decision-making compared with BPD participants with normal scores on the IGT (Maurex et al., 2009). Impaired decision-making was found to be a neuropsychological risk factor for suicidal behavior. Thus, these findings suggest that impaired decision-making in BPD may be associated with serotonin dysfunction and may be involved in suicidal behavior.

To clarify whether *TPH1* polymorphisms were related to BPD or to the high rates of suicidal behavior, Wilson et al. genotyped 100 BPD subjects and 101 healthy controls to examine the A218C polymorphism (rs1800532) in *TPH1* intron 7 and assessed subjects for impulsiveness and hostility (Wilson et al., 2009). The *TPH1* polymorphism was previously found to be associated with suicidal

behavior (Bellivier et al., 2004). In the study by Wilson et al., the A allele was significantly more frequent in the BPD group (AA/AC genotypes), and *TPH1* heterozygotes (AC) appeared to have the highest risk for BPD (p = 0.03). The suicide attempt status was not related to genotype in this patient group. These results suggest that the A allele of the *TPH1* A218C polymorphism may be associated with BPD and is not related to suicidal behavior in this sample (Wilson et al., 2009). This result was recently replicated in a sample of 398 patients with mood disorders. Patients with a diagnosis of BPD (n = 98) were more likely to be risk allele carriers (A allele) than non-BPD patients (Wilson et al., 2012). Another team genotyped 27 polymorphisms in seven serotonin genes in 113 Caucasian BPD patients and matched controls but failed to detect an association between *TPH1* and BPD (Ni et al., 2009). Aggregating these findings in a meta-analysis did not support a significant association between *TPH1* and BPD (see **Table 2**).

The *TPH2* gene has rarely been studied in the context of BPD. Since the identification of the *TPH2* gene (Zhou et al., 2005), an association between *TPH2* variants was found in 113 Caucasian BPD patients (Ni et al., 2009). Using 15 SNPs spanning a 106-kb region around *TPH2*, a "risk" haplotype was identified as being associated with anxiety, depression, and suicidal behavior. This "risk" haplotype was also moderately predictive of lower cerebrospinal fluid 5-HIAA concentrations in a sample of Caucasian Finnish individuals (Zhou et al., 2005), and interestingly, it was associated with BPD in an analysis of 103 healthy controls and 251 patients with personality disorders (including 109 patients with BPD) (Perez-Rodriguez et al., 2010). Subjects with the risk haplotype also exhibited higher aggression and emotional lability scores and increased suicidal behavior (Perez-Rodriguez et al., 2010).

Serotonin receptor genes

The serotonin 2A receptor gene (*HTR2A*) is considered as a candidate gene for BPD. Indeed, multiple lines of evidence suggest that this gene plays an important role in suicide, impulsive behavior, and emotional lability (Serretti et al., 2007).

To detect an association between *HTR2A* and BPD, four polymorphisms (rs6313 (T102C), rs4941573, rs2296972, and rs6314 (His452Tyr)) were genotyped in 111 Caucasian patients with BPD and 287 Caucasian controls. The results showed that the *HTR2A* gene is associated with personality traits, but not with BPD *per se* (Ni et al., 2006a).

In one study, 27 polymorphisms in seven serotonin genes were analyzed in 113 Caucasian BPD patients and matched controls, and the results were in favor of an association between BPD and the

HTR2C gene (Ni et al., 2009). In contrast, the *HTR1A, HTR1B, HTR1D,* and *HTR3A* genes showed no significant association with BPD, regardless of whether genotype, allele, or haplotype approaches were used. Lastly, significant interactions were detected between *HTR2C* and *TPH2*. Patients with the *HTR2C* rs6318G/G genotype had a higher frequency of the *TPH2* rs2171363C/T genotype compared with controls (Ni et al., 2009).

In a study coupling genetics and brain imaging, the *HTR1A* gene was genotyped in 25 patients and 25 controls (Zetzsche et al., 2008). No difference in allelic distribution between the groups was demonstrated. However, coupling these data with brain imaging showed that the volume of the amygdala of patients carrying the G allele was significantly lower than that of patients with a homozygous C/C genotype (Zetzsche et al., 2008). These results highlight the important role of the amygdala in BPD. In fact, excessive activation of the amygdala in response to emotional stimuli with negative valence in BPD has been demonstrated (Koenigsberg et al., 2009).

Lastly, four polymorphisms (SNPs) of the gene encoding the HTR1B receptor were genotyped in 161 Caucasian BPD patients and 156 healthy controls. No significant difference was demonstrated between the groups with respect to genotype or haplotype distribution (Tadić et al., 2009).

Serotonin transporter gene

The gene coding for the serotonin transporter (5-HTT or SLC6A4) is considered a candidate gene in many psychiatric disorders. Polymorphisms in this gene have been associated with suicide, impulsivity, addiction, and emotional lability (Gorwood et al., 2000).

In the first association study between BPD and the serotonin transporter gene, 89 Caucasian patients with BPD and 269 healthy Caucasian controls were genotyped for three common polymorphisms: variable number of tandem repeat (VNTR) polymorphisms in the serotonin-transporter-linked promoter region (5-HTTLPR) with short (S) and long (L) alleles, a single nucleotide variant (A/G) within the LPR region, and a VNTR in intron 2 (STin2) (Ni et al., 2006b). Significant differences in the allele frequencies of the VNTR marker and haplotype frequencies were detected between the patients and the controls. Patients with BPD showed a higher frequency of the 10-repeat VNTR marker and the S-10 haplotype and a lower frequency of the 12-repeat allele and the L_A-12 haplotype compared with healthy controls (Ni et al., 2006b). However, this association between the serotonin transporter gene and BPD has never been replicated, except in a study on 21 women with BPD from an initial sample of 90 women with bulimic syndromes (Steiger et al., 2007). In an association study of 86 BPD patients and 100 healthy controls, no association was reported for

the 5-HTTLPR and VNTR polymorphisms of the serotonin transporter gene (Pascual et al., 2008). Moreover, no difference in 5-HTTLPR genotype distributions was observed between 161 BPD patients and 156 healthy controls (Tadic et al., 2009). To extend these results, the functional A/G SNP within the long allele of the 5-HTTLPR (rs25531) and the variant STin2 were genotyped in the same population; again, no association was detected (Tadić et al., 2010). Such conflicting findings in examinations of the *5-HTT* gene led us to perform a meta-analysis. The results of this analysis indicated that there was no association between BPD and *5-HTT* (See **Table 2**).

INSERT TABLE 2 ABOUT HERE

Several other studies have been performed using a strategy based on dimensional traits. To determine the association between 5-HTTLPR and VNTR polymorphisms of *5-HTT* and personality traits in BPD, 65 patients with BPD were genotyped (5-HTTLPR in the promoter region and a VNTR in intron 2 (STin2)). Patients with the L allele (L/S or L/L) in the 5-HTTLPR region had lower scores on the subscale of "liking parties and friends" of the *Zuckerman-Kuhlman Personality Questionnaire*. Patients with the 10-repeat allele of the STin2 polymorphism had lower impulsivity, sensation seeking, and "liking parties and friends" scores (Pascual et al., 2007). Genotyping of the 5-HTTLPR among 32 young adults with BPD or antisocial personality disorder (APD) features with low-to-moderate income showed that the s allele was significantly related to BPD or APD traits (Lyons-Ruth et al., 2007). A study of 77 women with BPD that examined the association between 5-HTTLPR and clinical features of BPD (e.g., depressive disorder, anxious disorder, suicidal attempts, or self harm) reported that patients with the SS genotype had higher levels of borderline, depressive, anxious, and obsessive-compulsive traits, but no suicidal or self-injury behaviors, compared with patients carrying the L allele (Maurex et al., 2010).

Silva et al. analyzed the influence of the serotoninergic system in BPD using a pharmacogenetic approach. Fifty-nine patients with BPD and without any axis 1 disorders were treated with fluoxetine for 12 weeks and were compared for short versus long polymorphism of the 5-HTTLPR. The results showed that patients carrying the LL genotype had a better response to treatment and showed a reduction in aggressiveness and irritability compared with S carriers (Silva et al., 2007).

Monoamine oxidase A gene

Different polymorphisms within the gene encoding monoamine oxidase A (MAOA), which is involved in the degradation of serotonin and norepinephrine, have been associated with aggressive behavior and impulsivity (Craig and Halton, 2009). A total of 111 patients with BPD and 289 controls

were genotyped for two markers in the *MAOA* gene: a VNTR in the promoter and the rs6323 (T941G) SNP in exon 8. High-activity VNTR alleles were more frequently identified in BPD patients (Ni et al., 2007).

3.4.2. Dopaminergic system

There are several lines of evidence indicating that dopamine (DA) dysfunction may be associated with BPD. For example, human and animal studies indicate that DA pathways play an important role in several dimensions of BPD, notably in emotion information processing, impulse control, and cognition (Friedel, 2004). Furthermore, antipsychotic agents have been found to be efficient for reducing the core pathological symptoms of BPD (Lieb et al., 2010). However, very few studies have been performed to examine the genetic aspects of BPD.

In 2006, Joyce et al. recruited 334 patients with major depressive disorder from two treatment trials. A total of 22 and 21 patients with BPD were identified in each trial. Both groups showed a significant association between the 9-repeat allele of the dopamine transporter gene (*DAT1*) and BPD (Joyce et al., 2006).

In a dimensional approach, Nemoda et al. genotyped different polymorphisms in three dopaminergic genes in 99 young adults from low-to-moderate income families who were assessed for BPD and antisocial traits (Nemoda et al., 2010). BPD was assessed in a second independent group of patients with bipolar or major depressive disorder. The TaqI B1 allele and A1 allele in the *DRD2* gene, which encodes the dopamine receptor D2, and the promoter variant -616 of the *DRD4* gene, which encodes the dopamine receptor D4, were associated with borderline traits in the young adult sample. However, only the association with the promoter polymorphism of the *DRD4* gene was replicated in the independent sample. No association was found for any of the polymorphisms in the *catechol-O-methyltransferase* (*COMT*) gene, which encodes the enzyme that catabolizes dopamine, or the *DAT1* gene (Nemoda et al., 2010).

Catechol-O-methyltransferase gene

The protein encoded by the *COMT* gene is an enzyme (COMT) that breaks down dopamine. The rs4680 SNP in this gene is a missense mutation that causes the change of valine to methionine, which has a direct effect on enzyme activity. Subjects with the Val-Val genotype have fourfold increased activity compared with subjects with the Met-Met genotype (Calati et al., 2011). The *COMT* Val158Met/rs4680 SNP was genotyped in 161 patients with BPD and 156 controls. In BPD

patients, the Met/Met genotype was over-represented compared with healthy controls. This genotype was observed more frequently in BPD patients carrying at least one 5-HTTLPR S allele (Tadic et al., 2009), indicating the possibility of interactions between dopaminergic and serotonergic neurotransmission in the etiology of BPD.

Tyrosine hydroxylase (TH) is the rate-limiting enzyme for the synthesis of catecholamines and the conversion of L-tyrosine to L-DOPA. The *TH* Val81Met variant was genotyped in 156 Caucasian BPD patients and 152 healthy controls. A slight over-representation of the Met/Met genotype was found in BPD patients compared with controls. However, this association was below the significance level when multiple test correction was applied (Tadić et al., 2010).

3.4.3. Other genes

Brain Derived Neurotrophic Factor (BDNF) is a trophic factor involved in brain neurogenesis, synaptogenesis, and serotonin regulation (Martinowich and Lu, 2007). Some SNPs in the *BDNF* gene appear to be involved in several psychiatric disorders (Bath and Lee, 2006). The functional G196A SNP (substitution of a valine with a methionine at codon 66; rs6265) was genotyped in 161 patients with BPD and 156 controls, and no significant difference in its distribution was observed (Tadić et al., 2009).

Ten polymorphisms in the *SCNA9* gene, which encodes a sodium channel expressed in the hippocampus, were compared between 161 borderline patients and 156 healthy controls. No statistically significant association was demonstrated between these polymorphisms and BPD (Tadić et al., 2008).

Oxytocin and vasopressin play crucial roles in the regulation of attachment behaviors and thus may be altered in BPD, in which perceived rejection and loss often serve as triggers for impulsive, suicidal, and self-injurious behaviors (Stanley and Siever, 2010). Arginine vasopressin receptor 1A, encoded by the *AVPR1A* gene, is involved in attachment, and its neuropeptide might be involved in the interpersonal dimensions of BPD. A microsatellite polymorphism in the *AVPR1A* gene was analyzed in 161 BPD patients and 157 age- and sex-matched controls; however, no association was reported (Vogel et al., 2012).

Recently, the association of 23 SNPs in the neurexin 3 (*NRXN3*) gene with BPT was tested in heroin-dependent cases and controls; however, no association was found after correction for multiple testing (Panagopoulos et al., 2013).

Lastly, the first genome-wide association study (GWAS) of BPT, in which two Dutch cohorts (N=7125) were assessed with the PAI-BOR, revealed a signal on chromosome 5 corresponding to the SERINC5 protein, which is involved in myelination. This result was confirmed via replication in a third independent Dutch cohort (N=1301) (Lubke et al., 2013).

3.5. MOLECULAR STUDIES ON GENE-ENVIRONMENT INTERACTIONS

The few molecular genetic studies that have examined gene-environment interactions in BPD are summarized in **Table 3.** A review was recently published on this topic (Carpenter et al., 2013).

INSERT TABLE 3 ABOUT HERE

Wagner et al. adopted the gene-environment interaction paradigm to analyze the modulatory effects of different polymorphisms on the association between serious life events (e.g., experience of war, physical maltreatment, childhood sexual abuse, and severe accidents) and impulsive aggressive behavior in a cohort of 150 patients with BPD. Studying the serotonin transporter gene (5-HTTLPR), they showed that serious life events were associated with a decrease in impulsivity in SS and SL genotypes (Wagner et al., 2009). Childhood sexual abuse was previously shown to decrease impulsive aggression in BPD patients with the *BDNF* rs6265 Val/Val genotype (Wagner et al., 2009). Furthermore, 112 female BPD patients from the same sample were genotyped for the rs4680 *COMT* polymorphism. In the Val/Val genotype, but not the Val/Met and Met/Met genotypes, childhood sexual abuse was associated with lower impulsive aggression (Wagner et al., 2009). However, the *COMT* Val/Met polymorphism did not have modulatory effects on the association of serious life events (SLE) and impulsivity in a more recent study examining 159 patients with BPD (Wagner et al., 2010).

To highlight the mechanism by which a history of abuse may influence the risk for BPD, Wilson et al. genotyped 398 patients with mood disorders, assessing the *TPH1* G-6526A promoter polymorphism (rs4537731) and the A218C intron 7 polymorphism (rs1800532). Compared with non-BPD subjects, BPD patients were more likely to carry the A allele at both loci. The risk-allele carriers with a history of childhood abuse showed an increased probability of BPD diagnosis (Wilson et al., 2009).

4. DISCUSSION AND PROPOSAL FOR AN INTEGRATIVE MODEL

The existence of a genetic component in the genesis of BPD is largely supported. Indeed, despite discrepancies in the results of the first twin studies, several recent reports, including one performed across three countries (The Netherlands, Belgium, and Australia), have consistently estimated heritability to be approximately 40%, and two studies proposed heritabilities above 60% (Torgersen et al., 2012, 2000). Moreover, studies using genetic models based on large twin cohorts provided evidence of both G x E and gene–environment correlation (Distel et al., 2010) and showed that genetic and environmental effects influence the four main dimensions of BPD (Distel et al., 2010). It is important to note that clinical assessments differ between different twin study designs. As mentioned, classic twin studies used structured interview assessments with a limited number of BPD patients, while extended twin studies have used self-reporting with a wide range of subjects from the general population. The first GWAS on BPT (Lubke et al., 2013) was also performed using subjects from the general population assessed by a self-report (PAI-BOR). A signal was identified on chromosome 5, a region that includes the gene coding for the protein SERINC5 (involved in myelination), and the authors argued that reduced myelination may be associated with psychiatric disorders characterized by lack of social interaction. These results appear quite astonishing from a clinical perspective. Indeed, BPD is characterized by frantic efforts to avoid abandonment and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation (Lieb et al., 2004b). Thus, even if structured interview assessments and self-reports are correlated in BPD (Hopwood et al., 2008; Kurtz and Morey, 2001), this example shows that it is difficult to apply the results obtained from the general population assessed by self-reports to clinical populations.

Association studies using the candidate gene method have been disappointing. The number of such studies is surprisingly low considering both the heritability and the high frequency of BPD in the general population. Accordingly, isolated positive results from these studies have not been confirmed and therefore cannot lead to definite conclusions. Use of a fixed random-effects meta-analysis procedure revealed the absence of a statistically significant association between a given polymorphism and BPD (see **Table 2**). Our findings are compatible with the recent review by Calati and colleagues (Calati et al., 2013).

There are several explanations that may account for this lack of results. First, the available published studies involve relatively small samples. Second, BPD is most likely characterized by large clinical heterogeneity with frequent comorbidities (Mak and Lam, 2013), which are potentially driven

by multiple genes. Lastly, the influence of the environment is rarely taken into account in the majority of studies, although the presence of a G x E (or gene–environment correlation) is highly likely.

Another possible reason for the lack of susceptibility genes related to BPD may be due to the choice of candidate genes; indeed, there is a tendency to look for genetic effects on disease rather than genetic effects on vulnerability to environmental causes of disease (Caspi et al., 2010).

We believe that such a conceptual shift may affect the choice of new candidate genes in BPD. Genes associated with the physiological response to stress in the hypothalamic–pituitary–adrenal (HPA) axis are natural candidates for G x E research in BPD. In fact, many arguments support HPA axis dysregulation in BPD (Carrasco et al., 2007; Lieb et al., 2004a; Wingenfeld et al., 2010, 2007); however, the genes implicated in its regulation are particularly poorly studied. Moreover, it is interesting to note that epigenetic modifications have been identified in glucocorticoid receptor genes in patients with BPD. Epigenetics, which involves the study of changes in gene expression that occur without a change in the DNA sequence, is one of the molecular mechanisms underlying gene-environment interactions. Perroud and colleagues studied epigenetic modifications of the glucocorticoid receptor gene *NR3C1* in 101 BPD and 99 major depressive disorder (MDD) subjects and 15 MDD subjects with comorbid post-traumatic stress disorder (PTSD) (Perroud et al., 2011). Childhood abuse, which is highly prevalent in BPD, is mediated by the HPA axis and has been associated with increased methylation of exon 1F of *NR3C1* in subjects who experienced early adverse life events (McGowan et al., 2009). Thus, Perroud et al. showed that in BPD, the repetition of abuse and sexual abuse with penetration were correlated with a higher percentage of methylation in *NR3C1*. Similarly, women with bulimia nervosa and comorbid BPD showed significantly more *NR3C1* methylation (Steiger et al., 2013). Interestingly, using brain imaging techniques, some studies have revealed that BPD is associated with fronto-limbic dysfunctions and reductions in the volumes of the hippocampus and amygdala when compared with healthy controls. Such alterations are considered to be associated with HPA axis dysregulation (O'Neill and Frodl, 2012) and with the core symptoms of BPD (Hughes et al., 2012). From this perspective, the coupling of imaging and genetic approaches appears particularly suited for exploring the HPA axis dysregulation in BPD.

The idea that the identified genes should not be qualified as "vulnerability genes" but rather as "susceptibility to the environment genes" leads to a second conceptual shift in BPD research. In fact, "vulnerability genes" may function more like "plasticity genes", resulting in greater susceptibility of individuals to both positive (e.g., environmental support and enrichment) and negative (e.g.,

childhood maltreatment) facets of environmental experiences (Belsky et al., 2009). For example, individuals carrying the S variant of the 5-HTTLPR, considered to be a vulnerability gene for anxiety-related traits and increased emotionality, outperform subjects carrying the long allele when asked to perform some cognitive tasks (e.g., decision making, creative dance performance, attentional set-shifting) and show increased social conformity (for a review, see Homberg and Lesch, 2011). Thus, considering 5-HTTLPR as a plasticity gene rather than as a vulnerability gene leads us to suggest that environmental conditions determine whether a response will be negative (emotional) or positive (cognitive, in conformity with the social group) (Homberg and Lesch, 2011). Moreover, much of the available research investigating G x E focuses on negative environments and has failed to adequately measure positive environments (Belsky and Pluess, 2009). Thus, environmental factors in BPD are complex and can be represented as a balance of so-called negative and positive factors, as mentioned previously. This notion may explain the absence of an association between BPD and plasticity genes, such as 5-HTTLPR, serotonin receptors, tryptophan hydroxylase, and BDNF.

Plasticity genes are thus associated with increased sensitivity to the environment, for better or worse (Belsky et al., 2009). In our model (**Figure 2**), interactions exist throughout development between biological factors (e.g., epigenetic modification, fronto-limbic dysfunction, the HPA axis) and environmental factors, corresponding to a tightly controlled balance between positive and negative events. If the "environmental balance" is in favor of negative events during childhood, plasticity genes, corresponding in this case, to susceptibility genes to the environment, will contribute to impulsivity and emotional dysregulation. Indeed, most plasticity genes have been associated (Belsky and Pluess, 2009; Waider et al., 2011) with clinical dimensions that correspond to the core symptoms of BPD: impulsivity and emotional dysregulation leading to psychosocial conflicts and deficits, which may in turn reinforce impulsivity and emotional dysregulation (Lieb et al., 2004b; Skodol et al., 2002b). To reduce or avoid intense or negative effects, individuals develop maladaptive behaviors (e.g., self-harm, substance abuse, angry behavior) (Linehan, 1993). In a predominantly negative environment, repetition of these clinical features and maladaptive behaviors will be reinforced (Crowell et al., 2009). This mechanism may also apply to interpersonal difficulties associated with BPD, such as in the case of parents (or caregivers) of a child or adolescent with BPD who respond adversely to a needy or angry child, finally leading to an escalating series of negative interactions (Gunderson and Lyons-Ruth, 2008). Interestingly, the reinforcement and repetition of behaviors involves experience-dependent plasticity regulated by neurotransmitter systems associated with plasticity genes and corticostriatal circuits (Langen et al., 2011), which can influence behaviors and cognitive activity.

From our perspective, BPD is defined when behavioral flexibility is minimal and repetitiveness is maximal, as conceptualized for pathological repetitive behaviors (Graybiel, 2008). Prior to this ultimate stage, modification of the balance leading to a predominantly positive environment through interaction with plasticity genes could lead to other consequences aside from BPD, such as a risk of psychopathology in general or even no psychopathology (Hengartner et al., 2013). Interestingly, this conception offers the possibility that alternative outcomes other than BPD might result from the interaction between childhood abuse and genetic factors. Such a hypothesis naturally fits with the biosocial developmental model of BPD, which presents several biological vulnerabilities and environmental risk factors, many of which may increase the risk of developing other psychiatric disorders (e.g., mood disorders) (Crowell et al., 2009). Lastly, this model suggests that therapeutic interventions should occur as early as possible in the case of emotional deregulation, maladaptive behaviors, or BPD. At all stages, interventions should promote environmental support and struggle against the repetition of maladaptive behaviors.

INSERT FIGURE 2 ABOUT HERE

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 with large samples. Another way to improve upcoming studies in the field will be to explore dimensions and refined phenotypes in BPD rather than to look for an association with the entire disorder (Reichborn-Kjennerud, 2010). In fact, BPD has a potentially high clinical heterogeneity. For example, with nine DSM-IV criteria and a threshold of five positive criteria for a diagnosis of BPD, there are 151 theoretically possible ways of diagnosing this disorder (Skodol et al., 2002a). Moreover, BPD has been associated with many comorbidities, including mood disorders, anxiety disorders, and PTSD, and these comorbidities differ between men and women. Men more often display substance use disorders, and women more frequently present affective, anxiety, and eating disorders (Tadić et al., 2009; Zanarini et al., 1998). Thus, to refine the group of studied patients, it may be useful to perform studies on the clinical dimensions of BPD, such as impulsivity (Robbins et al., 2012), suicidality or severity of BPD (Moran and Crawford, 2013). Hallucination is another clinical dimension that could be investigated given its high frequency in BPD (approximately 40%) (Kingdon et al., 2010). In fact, this phenotype has yielded interesting results regarding the genetics of schizophrenia (Sanjuán et al.,

2013). Lastly, coupling methods may also improve comprehension of the involvement of genetic factors in BPD. The most popular coupling method corresponds to imaging genetics, a discipline that explores the neural pathways that translate genomic variation into complex psychiatric phenotypes. This strategy has proven to be powerful for identifying the mechanisms linking genes to behaviors and psychiatric diseases (Tost et al., 2012). For example, the first imaging genetics study related to BPD was performed to assess pain processing. In fact, BPD has been associated with reduced pain sensitivity in conjunction with self-injurious behavior. In BPD patients, this study showed a positive correlation between the number of Val alleles of the COMT gene and the level of brain activation in regions of affective processing, such as the anterior insula (Schmahl et al., 2012). Another key point that should be addressed in future research is the improvement of environmental factor measurement. According to our model, negative as well as positive environments should be measured. Furthermore, when examining environmental factors, developmental considerations should also be taken into account because their effect may be limited to certain sensitive periods. Measures should be taken repeatedly to enhance the power for detecting G x E. Lastly, even if collecting prospective data during a longitudinal study is the gold standard, retrospective reports can be performed using methods such as the life-history calendar method, which utilizes a month-to-month grid to facilitate accurate and rapid recall (Moffitt et al., 2006). Recommendations for future research are summarized in **box 1**.

In conclusion, the existence of a genetic vulnerability to BPD is largely supported by this review. We showed that G x E and gene-environment correlations were likely to play a role in the genesis of BPD. Association studies are currently sparse, and the current meta-analysis did not identify a susceptibility gene that can be implicated in the genesis of BPD. We completed this quantitative literature review by providing an integrative model of the genesis of BPD. In this model, genes were conceptualized as "plasticity genes" that interact with the childhood environment rather than as "vulnerability genes" for BPD. Beyond the idea of genes being systematically associated with the disorder, our model offers a dual perspective by considering genes in which expression can be modulated by negative as well as positive life events. Such a model may aid in the development of new avenues of research focused on the genesis of BPD, including the study of new candidate genes, brain imaging, and the assessment of different facets of the environment.

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REFERENCES

Bandelow, B., Krause, J., Wedekind, D., Broocks, A., Hajak, G., Rüther, E., 2005. Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with borderline personality disorder and healthy controls. Psychiatry Res. 134, 169–179.

Baron, M., Gruen, R., Asnis, L., Lord, S., 1985. Familial transmission of schizotypal and borderline personality disorders. Am. J. Psychiatry 142, 927–934.

Bath, K.G., Lee, F.S., 2006. Variant BDNF (Val66Met) impact on brain structure and function. Cogn. Affect. Behav. Neurosci. 6, 79–85.

Bax, L., Yu, L.-M., Ikeda, N., Moons, K.G., 2007. A systematic comparison of software dedicated to meta-analysis of causal studies. BMC Med. Res. Methodol. 7, 40.

Bellivier, F., Chaste, P., Malafosse, A., 2004. Association between the TPH gene A218C polymorphism and suicidal behavior: a meta-analysis. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 124B, 87–91.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R., 2009. Vulnerability genes or plasticity genes. Mol Psychiatry 14, 746–754.

Belsky, J., Pluess, M., 2009. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol. Bull. 135, 885–908.

Bierer, L.M., Yehuda, R., Schmeidler, J., Mitropoulou, V., New, A.S., Silverman, J.M., Siever, L.J., 2003. Abuse and neglect in childhood: relationship to personality disorder diagnoses. CNS Spectr. 8, 737–754.

Boomsma, D., Busjahn, A., Peltonen, L., 2002. Classical twin studies and beyond. Nat. Rev. Genet. 3, 872–882.

Bornovalova, M.A., Hicks, B.M., Iacono, W.G., McGue, M., 2009. Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: a longitudinal twin study. Dev. Psychopathol. 21, 1335–1353.

Calati, R., Gressier, F., Balestri, M., Serretti, A., 2013. Genetic modulation of borderline personality disorder: Systematic review and meta-analysis. J. Psychiatr. Res.

Calati, R., Porcelli, S., Giegling, I., Hartmann, A.M., Möller, H.-J., De Ronchi, D., Serretti, A., Rujescu, D., 2011. Catechol-o-methyltransferase gene modulation on suicidal behavior and personality traits: review, meta-analysis and association study. J. Psychiatr. Res. 45, 309–321.

Carpenter, R.W., Tomko, R.L., Trull, T.J., Boomsma, D.I., 2013. Gene-Environment Studies and Borderline Personality Disorder: A Review. Curr. Psychiatry Rep. 15, 1–7.

Carrasco, J.L., Diaz-Marsa, M., Pastrana, J.I., Molina, R., Brotons, L., Lopez-Ibor, M.I., Lopez-Ibor, J.J., 2007. Hypothalamic-pituitary-adrenal axis response in borderline personality disorder without post-traumatic features. Br. J. Psychiatry 190, 357–358.

Caspi, A., Hariri, A.R., Holmes, A., Uher, R., Moffitt, T.E., 2010. Genetic Sensitivity to the Environment: The Case of the Serotonin Transporter Gene and Its Implications for Studying Complex Diseases and Traits. Am. J. Psychiatry 167, 509–527.

Costa, P.T., MacCrae, R.R., 1992. Revised NEO Personality Inventory (NEO PI-R) and NEO Five-Factor Inventory (NEO FFI): Professional Manual. Psychological Assessment Resources.

Craig, I.W., Halton, K.E., 2009. Genetics of human aggressive behaviour. Hum. Genet. 126, 101–113.

Crowell, S.E., Beauchaine, T.P., Linehan, M.M., 2009. A biosocial developmental model of borderline personality: Elaborating and extending linehan's theory. Psychol. Bull. 135, 495–510.

De Moor, M.H.M., Distel, M.A., Trull, T.J., Boomsma, D.I., 2009. Assessment of borderline personality features in population samples: is the Personality Assessment Inventory-Borderline Features scale measurement invariant across sex and age? Psychol. Assess. 21, 125–130.

Distel, M., Rebollo-Mesa, I., Willemsen, G., Derom, C.A., Trull, T.J., Martin, N.G., Boomsma, D.I., 2009a. Familial resemblance of borderline personality disorder features: genetic or cultural transmission? PloS One 4, e5334.

Distel, M., Roeling, M.P., Tielbeek, J.J., van Toor, D., Derom, C.A., Trull, T.J., Boomsma, D.I., 2012a. The covariation of trait anger and borderline personality: a bivariate twin-siblings study. J. Abnorm. Psychol. 121, 458–466.

Distel, M., Trull, T.J., de Moor, M.M.H., Vink, J.M., Geels, L.M., van Beek, J.H.D.A., Bartels, M., Willemsen, G., Thiery, E., Derom, C.A., Neale, M.C., Boomsma, D.I., 2012b. Borderline personality traits and substance use: genetic factors underlie the association with smoking and ever use of cannabis, but not with high alcohol consumption. J. Personal. Disord. 26, 867–879.

Distel, M., Trull, T.J., Willemsen, G., Vink, J.M., Derom, C.A., Lynskey, M., Martin, N.G., Boomsma, D.I., 2009b. The five-factor model of personality and borderline personality disorder: a genetic analysis of comorbidity. Biol. Psychiatry 66, 1131–1138.

Distel, M., Willemsen, G., Ligthart, L., Derom, C.A., Martin, N.G., Neale, M.C., Trull, T.J., Boomsma, D.I., 2010. Genetic covariance structure of the four main features of borderline personality disorder. J. Personal. Disord. 24, 427–444.

Distel, M.A., Carlier, A., Middeldorp, C.M., Derom, C.A., Lubke, G.H., Boomsma, D.I., 2011. Borderline personality traits and adult attention-deficit hyperactivity disorder symptoms: A genetic analysis of comorbidity. Am. J. Med. Genet. B Neuropsychiatr. Genet. 156, 817–825.

Distel, M.A., Hottenga, J.-J., Trull, T.J., Boomsma, D.I., 2008a. Chromosome 9: linkage for borderline personality disorder features. Psychiatr. Genet. 18, 302–7.

Distel, M.A., Middeldorp, C.M., Trull, T.J., Derom, C.A., Willemsen, G., Boomsma, D.I., 2010. Life events and borderline personality features: the influence of gene-environment interaction and gene-environment correlation. Psychol. Med. 1–12.

Distel, M.A., Trull, T.J., Derom, C.A., Thiery, E.W., Grimmer, M.A., Martin, N.G., Willemsen, G., Boomsma, D.I., 2008b. Heritability of borderline personality disorder features is similar across three countries. Psychol. Med. 38, 1219–1229.

Fossati, A., Madeddu, F., Maffei, C., 1999. Borderline Personality Disorder and childhood sexual abuse: a meta-analytic study. J. Personal. Disord. 13, 268–280.

Friedel, R.O., 2004. Dopamine dysfunction in borderline personality disorder: a hypothesis. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 29, 1029–1039.

Gabbard, G.O., 2005. Mind, Brain, and Personality Disorders. Am J Psychiatry 162, 648–655.

Gorwood, P., Batel, P., Adès, J., Hamon, M., Boni, C., 2000. Serotonin transporter gene polymorphisms, alcoholism, and suicidal behavior. Biol. Psychiatry 48, 259–264.

Grant, B.F., Chou, S.P., Goldstein, R.B., Huang, B., Stinson, F.S., Saha, T.D., Smith, S.M., Dawson, D.A., Pulay, A.J., Pickering, R.P., Ruan, W.J., 2008. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry 69, 533–545.

Graybiel, A.M., 2008. Habits, rituals, and the evaluative brain. Annu Rev Neurosci 31, 359–387.

Gunderson, J.G., Lyons-Ruth, K., 2008. BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model. J. Personal. Disord. 22, 22–41.

Gunderson, J.G., Zanarini, M.C., Choi-Kain, L.W., Mitchell, K.S., Jang, K.L., Hudson, J.I., 2011. Family Study of Borderline Personality Disorder and Its Sectors of Psychopathology. Arch Gen Psychiatry 68, 753–762.

Hengartner, M.P., Müller, M., Rodgers, S., Rössler, W., Ajdacic-Gross, V., 2013. Can protective factors moderate the detrimental effects of child maltreatment on personality functioning? J. Psychiatr. Res. 47, 1180–1186.

Homberg, J.R., Lesch, K.-P., 2011. Looking on the Bright Side of Serotonin Transporter Gene Variation. Biol. Psychiatry 69, 513–519.

Hopwood, C.J., Morey, L.C., Edelen, M.O., Shea, M.T., Grilo, C.M., Sanislow, C.A., McGlashan, T.H., Daversa, M.T., Gunderson, J.G., Zanarini, M.C., Markowitz, J.C., Skodol, A.E., 2008. A comparison of interview and self-report methods for the assessment of borderline personality disorder criteria. Psychol. Assess. 20, 81–85.

Hughes, A.E., Crowell, S.E., Uyeji, L., Coan, J.A., 2012. A Developmental Neuroscience of Borderline Pathology: Emotion Dysregulation and Social Baseline Theory. J. Abnorm. Child Psychol. 40, 21–33.

Johnson, B.A., Brent, D.A., Connolly, J., Bridge, J., Matta, J., Constantine, D., Rather, C., White, T., 1995. Familial aggregation of adolescent personality disorders. J. Am. Acad. Child Adolesc. Psychiatry 34, 798–804.

Joyce, P.R., McHugh, P.C., McKenzie, J.M., Sullivan, P.F., Mulder, R.T., Luty, S.E., Carter, J.D., Frampton, C.M.A., Robert Cloninger, C., Miller, A.M., Kennedy, M.A., 2006. A dopamine transporter polymorphism is a risk factor for borderline personality disorder in depressed patients. Psychol. Med. 36, 807–813.

Kendler, K.S., Aggen, S.H., Czajkowski, N., Roysamb, E., Tambs, K., Torgersen, S., Neale, M.C., Reichborn-Kjennerud, T., 2008. The Structure of Genetic and Environmental Risk Factors for DSM-IV Personality Disorders: A Multivariate Twin Study. Arch Gen Psychiatry 65, 1438–1446.

Kendler, K.S., Eaves, L.J., 1986. Models for the joint effect of genotype and environment on liability to psychiatric illness. Am. J. Psychiatry 143, 279–289.

Kendler, K.S., Myers, J., Potter, J., Opalesky, J., 2009. A Web-Based Study of Personality, Psychopathology and Substance Use in Twin, Other Relative and Relationship Pairs. Twin Res. Hum. Genet. 12, 137–141.

Kendler, K.S., Myers, J., Reichborn-Kjennerud, T., 2011. Borderline personality disorder traits and their relationship with dimensions of normative personality: a web-based cohort and twin study. Acta Psychiatr. Scand. 123, 349–359.

Kingdon, D.G., Ashcroft, K., Bhandari, B., Gleeson, S., Warikoo, N., Symons, M., Taylor, L., Lucas, E., Mahendra, R., Ghosh, S., Mason, A., Badrakalimuthu, R., Hepworth, C., Read, J., Mehta, R., 2010. Schizophrenia and borderline

personality disorder: similarities and differences in the experience of auditory hallucinations, paranoia, and childhood trauma. J. Nerv. Ment. Dis. 198, 399–403.

Koenigsberg, H.W., Siever, L.J., Lee, H., Pizzarello, S., New, A.S., Goodman, M., Cheng, H., Flory, J., Prohovnik, I., 2009. Neural correlates of emotion processing in borderline personality disorder. Psychiatry Res. Neuroimaging 172, 192–199.

Kurtz, J.E., Morey, L.C., 2001. Use of structured self-report assessment to diagnose borderline personality disorder during major depressive episodes. Assessment 8, 291–300.

Langen, M., Durston, S., Kas, M.J., van Engeland, H., Staal, W.G., 2011. The neurobiology of repetitive behavior:… and men. Neurosci. Biobehav. Rev. 35, 356–365.

Leichsenring, F., Leibing, E., Kruse, J., New, A.S., Leweke, F., 2011. Borderline personality disorder. The Lancet 377, 74–84.

Lenzenweger, M.F., Lane, M.C., Loranger, A.W., Kessler, R.C., 2007. DSM-IV Personality Disorders in the National Comorbidity Survey Replication. Biol. Psychiatry 62, 553–564.

Lieb, K., Rexhausen, J.E., Kahl, K.G., Schweiger, U., Philipsen, A., Hellhammer, D.H., Bohus, M., 2004a. Increased diurnal salivary cortisol in women with borderline personality disorder. J. Psychiatr. Res. 38, 559–565.

Lieb, K., Vollm, B., Rucker, G., Timmer, A., Stoffers, J.M., 2010. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br. J. Psychiatry 196, 4–12.

Lieb, K., Zanarini, M.C., Schmahl, C., Linehan, M.M., Bohus, M., 2004b. Borderline personality disorder. The Lancet 364, 453–461.

Linehan, M., 1993. Cognitive-behavioral treatment of borderline personality disorder. The Guilford Press.

Links, P.S., Steiner, M., Huxley, G., 1988. The Occurrence of Borderline Personality Disorder in the Families of Borderline Patients. J. Personal. Disord. 2, 14–20.

Loranger, A.W., Oldham, J.M., Tulis, E.H., 1982. Familial transmission of DSM-III borderline personality disorder. Arch. Gen. Psychiatry 39, 795–799.

Lubke, G.H., Laurin, C., Amin, N., Hottenga, J.J., Willemsen, G., van Grootheest, G., Abdellaoui, A., Karssen, L.C., Oostra, B.A., van Duijn, C.M., Penninx, B.W.J.H., Boomsma, D.I., 2013. Genome-wide analyses of borderline personality features. Mol. Psychiatry.

Lyons-Ruth, K., Holmes, B.M., Sasvari-Szekely, M., Ronai, Z., Nemoda, Z., Pauls, D., 2007. Serotonin transporter polymorphism and borderline or antisocial traits among low-income young adults. Psychiatr. Genet. 17, 339–43.

Mak, A.D.P., Lam, L.C.W., 2013. Neurocognitive profiles of people with borderline personality disorder. Curr. Opin. Psychiatry 26, 90–96.

Martinowich, K., Lu, B., 2007. Interaction between BDNF and Serotonin: Role in Mood Disorders. Neuropsychopharmacology 33, 73–83.

Maurex, L., Zaboli, G., Öhman, A., Åsberg, M., Leopardi, R., 2010. The serotonin transporter gene polymorphism (5-HTTLPR) and affective symptoms among women diagnosed with borderline personality disorder. Eur. Psychiatry 25, 19–25.

Maurex, L., Zaboli, G., Wiens, S., Asberg, M., Leopardi, R., Ohman, A., 2009. Emotionally controlled decision-making and a gene variant related to serotonin synthesis in women with borderline personality disorder. Scand. J. Psychol. 50, 5–10.

McGloin, J.M., Widom, C.S., 2001. Resilience among abused and neglected children grown up. Dev. Psychopathol. 13, 1021–1038.

McGowan, P.O., Sasaki, A., D'Alessio, A.C., Dymov, S., Labonté, B., Szyf, M., Turecki, G., Meaney, M.J., 2009. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat. Neurosci. 12, 342–348.

Moffitt, T.E., Caspi, A., Rutter, M., 2006. Measured gene-environment interactions in psychopathology concepts, research strategies, and implications for research, intervention, and public understanding of genetics. Perspect. Psychol. Sci. 1, 5–27.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The PRISMA Group, 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6, e1000097.

Moran, P., Crawford, M.J., 2013. Assessing the severity of borderline personality disorder. Br. J. Psychiatry J. Ment. Sci. 203, 163–164.

Nemoda, Z., Lyons-Ruth, K., Szekely, A., Bertha, E., Faludi, G., Sasvari-Szekely, M., 2010. Association between dopaminergic polymorphisms and borderline personality traits among at-risk young adults and psychiatric inpatients. Behav. Brain Funct. 6, 4.

New, A.S., Triebwasser, J., Charney, D.S., 2008. The Case for Shifting Borderline Personality Disorder to Axis I. Biol. Psychiatry 64, 653–659.

Ni, X., Bismil, R., Chan, K., Sicard, T., Bulgin, N., McMain, S., Kennedy, J.L., 2006a. Serotonin 2A receptor gene is associated with personality traits, but not to disorder, in patients with borderline personality disorder. Neurosci. Lett. 408, 214–219.

Ni, X., Chan, D., Chan, K., McMain, S., Kennedy, J.L., 2009. Serotonin genes and gene-gene interactions in borderline personality disorder in a matched case-control study. Prog. Neuropsychopharmacol. Biol. Psychiatry 33, 128–33.

Ni, X., Chan, K., Bulgin, N., Sicard, T., Bismil, R., McMain, S., Kennedy, J.L., 2006b. Association between serotonin transporter gene and borderline personality disorder. J. Psychiatr. Res. 40, 448–453.

Ni, X., Sicard, T., Bulgin, N., Bismil, R., Chan, K., McMain, S., Kennedy, J.L., 2007. Monoamine oxidase a gene is associated with borderline personality disorder. Psychiatr. Genet. 17, 153–7.

O'Neill, A., Frodl, T., 2012. Brain structure and function in borderline personality disorder. Brain Struct. Funct. 217, 767–782.

Panagopoulos, V.N., Trull, T.J., Glowinski, A.L., Lynskey, M.T., Heath, A.C., Agrawal, A., Henders, A.K., Wallace, L., Todorov, A.A., Madden, P.A.F., Moore, E., Degenhardt, L., Martin, N.G., Montgomery, G.W., Nelson, E.C., 2013. Examining the association of NRXN3 SNPs with borderline personality disorder phenotypes in heroin dependent cases and socio-economically disadvantaged controls. Drug Alcohol Depend. 128, 187–193.

Paris, J., 1998. Does childhood trauma cause personality disorders in adults? Can. J. Psychiatry Rev. Can. Psychiatr. 43, 148–153.

Paris, J., 2007. The nature of borderline personality disorder: multiple dimensions, multiple symptoms, but one category. J. Personal. Disord. 21, 457–473.

Paris, J., Zweig-Frank, H., 1992. A critical review of the role of childhood sexual abuse in the etiology of borderline personality disorder. Can. J. Psychiatry Rev. Can. Psychiatr.

Paris, J., Zweig-Frank, H., Guzder, J., 1994. Psychological risk factors for borderline personality disorder in female patients. Compr. Psychiatry 35, 301–305.

Pascual, J.C., Soler, J., Baiget, M., Cortés, A., Menoyo, A., Barrachina, J., Ropero, M., Gomà, M., Alvarez, E., Perez, V., 2007. Association between the serotonin transporter gene and personality traits in borderline personality disorder patients evaluated with Zuckerman-Zuhlman Personality Questionnaire (ZKPQ). Actas Esp. Psiquiatr. 35, 382–386.

Pascual, J.C., Soler, J., Barrachina, J., Campins, M.J., Alvarez, E., Pérez, V., Cortés, A., Baiget, M., 2008. Failure to detect an association between the serotonin transporter gene and borderline personality disorder. J. Psychiatr. Res. 42, 87–88.

Perez-Rodriguez, M., Weinstein, S., New, A.S., Bevilacqua, L., Yuan, Q., Zhou, Z., Hodgkinson, C., Goodman, M., Koenigsberg, H.W., Goldman, D., Siever, L.J., 2010. Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. J. Psychiatr. Res. 44, 1075–1081.

Perroud, N., Paoloni-Giacobino, A., Prada, P., Olié, E., Salzmann, A., Nicastro, R., Guillaume, S., Mouthon, D., Stouder, C., Dieben, K., Huguelet, P., Courtet, P., Malafosse, A., 2011. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Transl. Psychiatry 1, e59.

Pope, H.G., Jr, Jonas, J.M., Hudson, J.I., Cohen, B.M., Gunderson, J.G., 1983. The validity of DSM-III borderline personality disorder. A phenomenologic, family history, treatment response, and long-term follow-up study. Arch. Gen. Psychiatry 40, 23–30.

Reich, J.H., 1989. Familiality of DSM-III dramatic and anxious personality clusters. J. Nerv. Ment. Dis. 177, 96–100.

Reichborn-Kjennerud, T., 2010. The genetic epidemiology of personality disorders. Dialogues Clin. Neurosci. 12, 103–114.

Reichborn-Kjennerud, T., Czajkowski, N., Røysamb, E., Ørstavik, R.E., Neale, M.C., Torgersen, S., Kendler, K.S., 2010. Major depression and dimensional representations of DSM-IV personality disorders: a population-based twin study. Psychol. Med. 40, 1475–1484.

Reichborn-Kjennerud, T., Ystrom, E., Neale, M.C., Aggen, S.H., Mazzeo, S.E., Knudsen, G.P., Tambs, K., Czajkowski, N.O., Kendler, K.S., 2013. Structure of Genetic and Environmental Risk Factors for Symptoms of DSM-IV Borderline Personality Disorder. JAMA Psychiatry Chic. Ill.

Riso, L.P., Klein, D.N., Anderson, R.L., Ouimette, P.C., 2000. A family study of outpatients with borderline personality disorder and no history of mood disorder. J. Personal. Disord. 14, 208–217.

Robbins, T.W., Gillan, C.M., Smith, D.G., Wit, S. de, Ersche, K.D., 2012. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. Trends Cogn. Sci. 16, 81–91.

Sanjuán, J., Moltó, M.D., Tolosa, A., 2013. Candidate Genes Involved in the Expression of Psychotic Symptoms: A Focus on Hallucinations, in: Jardri, R., Cachia, A., Thomas, P., Pins, D. (Eds.), The Neuroscience of Hallucinations. Springer New York, pp. 231–252.

Savelieva, K.V., Zhao, S., Pogorelov, V.M., Rajan, I., Yang, Q., Cullinan, E., Lanthorn, T.H., 2008. Genetic Disruption of Both Tryptophan Hydroxylase Genes Dramatically Reduces Serotonin and Affects Behavior in Models Sensitive to Antidepressants. PLoS ONE 3, e3301.

Schmahl, C., Ludäscher, P., Greffrath, W., Kraus, A., Valerius, G., Schulze, T.G., Treutlein, J., Rietschel, M., Smolka, M.N., Bohus, M., 2012. COMT val158met polymorphism and neural pain processing. PloS One 7, e23658.

Serretti, A., Drago, A., De Ronchi, D., 2007. HTR2A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. Curr. Med. Chem. 14, 2053–2069.

Silva, H., Iturra, P., Solari, A., Villarroel, J., Jerez, S., Vielma, W., Montes, C., Pumarino, L., Roa, N., 2007. Serotonin transporter polymorphism and fluoxetine effect on impulsiveness and aggression in borderline personality disorder. Actas Esp. Psiquiatr. 35, 387–392.

Skodol, A.E., 2005. Dimensional Representations of DSM-IV Personality Disorders: Relationships to Functional Impairment. Am. J. Psychiatry 162, 1919–1925.

Skodol, A.E., Gunderson, J.G., Pfohl, B., Widiger, T.A., Livesley, W.J., Siever, L.J., 2002a. The borderline diagnosis I: psychopathology, comorbidity, and personality structure. Biol. Psychiatry 51, 936–50.

Skodol, A.E., Siever, L.J., Livesley, W.J., Gunderson, J.G., Pfohl, B., Widiger, T.A., 2002b. The borderline diagnosis II: biology, genetics, and clinical course. Biol. Psychiatry 51, 951–63.

Stanley, B., Siever, L.J., 2010. The Interpersonal Dimension of Borderline Personality Disorder: Toward a Neuropeptide Model. Am J Psychiatry 167, 24–39.

Steiger, H., Labonté, B., Groleau, P., Turecki, G., Israel, M., 2013. Methylation of the glucocorticoid receptor gene promoter in bulimic women: Associations with borderline personality disorder, suicidality, and exposure to childhood abuse. Int. J. Eat. Disord.

Steiger, H., Richardson, J., Joober, R., Gauvin, L., Israel, M., Bruce, K.R., Ying Kin, N.M.. N., Howard, H., Young, S.N., 2007. The 5HTTLPR polymorphism, prior maltreatment and dramatic-erratic personality manifestations in women with bulimic syndromes. J. Psychiatry Neurosci. JPN 32, 354–362.

Stevenson, J., Meares, R., Comerford, A., 2003. Diminished Impulsivity in Older Patients With Borderline Personality Disorder. Am J Psychiatry 160, 165–166.

Stone, M.H., Kahn, E., Flye, B., 1981. Psychiatrically ill relatives of borderline patients: A family study. Psychiatr. Q. 53, 71–84.

Tadić, A., Baskaya, O., Victor, A., Lieb, K., Höppner, W., Dahmen, N., 2008. Association analysis of SCN9A gene variants with borderline personality disorder. J. Psychiatr. Res. 43, 155–63.

Tadić, A., Elsässer, A., Storm, N., Baade, U., Wagner, S., Başşkaya, O., Lieb, K., Dahmen, N., 2010. Association analysis between gene variants of the tyrosine hydroxylase and the serotonin transporter in borderline personality disorder. World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry 11, 45–58.

Tadić, André, Elsässer, A., Victor, A., von Cube, R., Başkaya, O., Wagner, S., Lieb, K., Höppner, W., Dahmen, N., 2009. Association analysis of serotonin receptor 1B (HTR1B) and brain-derived neurotrophic factor gene polymorphisms in Borderline personality disorder. J. Neural Transm. Vienna Austria 1996 116, 1185–1188.

Tadic, A., Victor, A., Baskaya, Ö., Cube, R. von, Hoch, J., Kouti, I., Anicker, N.J., Höppner, W., Lieb, K., Dahmen, N., 2009. Interaction between gene variants of the serotonin transporter promoter region (5-HTTLPR) and catechol O methyltransferase (COMT) in borderline personality disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. 150B, 487–495.

Tadić, A, Wagner, S., Hoch, J., Başkaya, O., von Cube, R., Skaletz, C., Lieb, K., Dahmen, N., 2009. Gender Differences in Axis I and Axis II Comorbidity in Patients with Borderline Personality Disorder. Psychopathology 42, 257–263.

Tomko, R.L., Trull, T.J., Wood, P.K., Sher, K.J., 2013. Characteristics of Borderline Personality Disorder in a Community Sample: Comorbidity, Treatment Utilization, and General Functioning. J. Personal. Disord. 1–17.

Torgersen, S., 1984. Genetic and nosological aspects of schizotypal and borderline personality disorders. A twin study. Arch. Gen. Psychiatry 41, 546–554.

Torgersen, S., Czajkowski, N., Jacobson, K., Reichborn-Kjennerud, T., Røysamb, E., Neale, M.C., Kendler, K.S., 2008. Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. Psychol. Med. 38, 1617–1625.

Torgersen, S., Lygren, S., Øien, P.A., Skre, I., Onstad, S., Edvardsen, J., Tambs, K., Kringlen, E., 2000. A twin study of personality disorders. Compr. Psychiatry 41, 416–425.

Torgersen, S., Myers, J., Reichborn-Kjennerud, T., Røysamb, E., Kubarych, T.S., Kendler, K.S., 2012. The Heritability of Cluster B Personality Disorders Assessed Both by Personal Interview and Questionnaire. J. Personal. Disord. 26, 848–866.

Tost, H., Bilek, E., Meyer-Lindenberg, A., 2012. Brain connectivity in psychiatric imaging genetics. NeuroImage 62, 2250–2260.

Trull, T.J., 2001. Relationships of borderline features to parental mental illness, childhood abuse, Axis I disorder, and current functioning. J. Personal. Disord. 15, 19–32.

Van Dongen, J., Slagboom, P.E., Draisma, H.H.M., Martin, N.G., Boomsma, D.I., 2012. The continuing value of twin studies in the omics era. Nat. Rev. Genet. 13, 640–653.

Vogel, F., Wagner, S., Başkaya, O., Leuenberger, B., Mobascher, A., Dahmen, N., Lieb, K., Tadić, A., 2012. Variable number of tandem repeat polymorphisms of the arginine vasopressin receptor 1A gene and impulsive aggression in patients with borderline personality disorder. Psychiatr. Genet. 22, 105–106.

Wagner, S, Baskaya, O., Anicker, N.J., Dahmen, N., Lieb, K., Tadić, A., 2009. The catechol o-methyltransferase (COMT) valmet polymorphism modulates the association of serious life events (SLE) and impulsive aggression in female patients with borderline personality disorder (BPD). Acta Psychiatr. Scand.

Wagner, S., Baskaya, Ö., Dahmen, N., Lieb, K., Tadi0107, A., 2009. Modulatory role of the brain-derived neurotrophic factor $Val^{66}Met$ polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes Brain Behav. 9999.

Wagner, Stefanie, Baskaya, O., Lieb, K., Dahmen, N., Tadić, A., 2009. The 5-HTTLPR polymorphism modulates the association of serious life events (SLE) and impulsivity in patients with Borderline Personality Disorder. J. Psychiatr. Res. 43, 1067–1072.

Wagner, S., Baskaya, Ö., Lieb, K., Dahmen, N., Tadic, A., 2010. Lack of modulating effects of the COMT Val158Met polymorphism on the association of serious life events (SLE) and impulsivity in patients with Borderline Personality Disorder. J. Psychiatr. Res. 44, 121–122.

Waider, J., Araragi, N., Gutknecht, L., Lesch, K.-P., 2011. Tryptophan hydroxylase-2 (TPH2) in disorders of cognitive control and emotion regulation: A perspective. Psychoneuroendocrinology 36, 393–405.

Wilson, S.T., Stanley, B., Brent, D.A., Oquendo, M.A., Huang, Y., Haghighi, F., Hodgkinson, C.A., Mann, J.J., 2012. Interaction between tryptophan hydroxylase I polymorphisms and childhood abuse is associated with increased risk for borderline personality disorder in adulthood. Psychiatr. Genet. 22, 15–24.

Wilson, S.T., Stanley, B., Brent, D.A., Oquendo, M.A., Huang, Y., Mann, J.J., 2009. The tryptophan hydroxylase-1 A218C polymorphism is associated with diagnosis, but not suicidal behavior, in borderline personality disorder. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 150B, 202–208.

Wingenfeld, K., Lange, W., Wulff, H., Berea, C., Beblo, T., Saavedra, A.S., Mensebach, C., Driessen, M., 2007. Stability of the dexamethasone suppression test in borderline personality disorder with and without comorbid PTSD: A one-year follow-up study. J. Clin. Psychol. 63, 843–850.

Wingenfeld, K., Spitzer, C., Rullkötter, N., Löwe, B., 2010. Borderline personality disorder: Hypothalamus pituitary adrenal axis and findings from neuroimaging studies. Psychoneuroendocrinology 35, 154–170.

Yen, S., Shea, M.T., Battle, C.L., Johnson, D.M., Zlotnick, C., Dolan-Sewell, R., Skodol, A.E., Grilo, C.M., Gunderson, J.G., Sanislow, C.A., Zanarini, M.C., Bender, D.S., Rettew, J.B., McGlashan, T.H., 2002. Traumatic exposure and posttraumatic stress disorder in borderline, schizotypal, avoidant, and obsessive-compulsive personality disorders: findings from the collaborative longitudinal personality disorders study. J. Nerv. Ment. Dis. 190, 510–518.

Zaboli, G., Gizatullin, R., Nilsonne, A., Wilczek, A., Jönsson, E.G., Ahnemark, E., Asberg, M., Leopardi, R., 2006. Tryptophan hydroxylase-1 gene variants associate with a group of suicidal borderline women. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 31, 1982–1990.

Zanarini, M.C., Frankenburg, F.R., Dubo, E.D., Sickel, A.E., Trikha, A., Levin, A., Reynolds, V., 1998. Axis I Comorbidity of Borderline Personality Disorder. Am. J. Psychiatry 155, 1733–1739.

Zanarini, M.C., Frankenburg, F.R., Reich, D.B., Silk, K.R., Hudson, J.I., McSweeney, L.B., 2007. The Subsyndromal Phenomenology of Borderline Personality Disorder: A 10-Year Follow-Up Study. Am J Psychiatry 164, 929–935.

Zanarini, M.C., Frankenburg, F.R., Yong, L., Raviola, G., Bradford Reich, D., Hennen, J., Hudson, J.I., Gunderson, J.G., 2004. Borderline psychopathology in the first-degree relatives of borderline and axis II comparison probands. J. Personal. Disord. 18, 439–447.

Zanarini, M.C., Gunderson, J.G., Marino, M.F., Schwartz, E.O., Frankenburg, F.R., 1988. DSM-III Disorders in the Families of Borderline Outpatients. J. Personal. Disord. 2, 292–302.

Zanarini, M.C., Williams, A.A., Lewis, R.E., Reich, R.B., Vera, S.C., Marino, M.F., Levin, A., Yong, L., Frankenburg, F.R., 1997. Reported pathological childhood experiences associated with the development of borderline personality disorder. Am. J. Psychiatry 154, 1101–1106.

Zanarini, M.C., Yong, L., Frankenburg, F.R., Hennen, J., Reich, D.B., Marino, M.F., Vujanovic, A.A., 2002. Severity of reported childhood sexual abuse and its relationship to severity of borderline psychopathology and psychosocial impairment among borderline inpatients. J. Nerv. Ment. Dis. 190, 381–387.

Zetzsche, T., Preuss, U.W., Bondy, B., Frodl, T., Zill, P., Schmitt, G., Koutsouleris, N., Rujescu, D., Born, C., Reiser, M., Möller, H.-J., Meisenzahl, E.M., 2008. 5-HT1A receptor gene C -1019 G polymorphism and amygdala volume in borderline personality disorder. Genes Brain Behav. 7, 306–13.

Zhou, Z., Roy, A., Lipsky, R., Kuchipudi, K., Zhu, G., Taubman, J., Enoch, M.-A., Virkkunen, M., Goldman, D., 2005. Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. Arch. Gen. Psychiatry 62, 1109–1118.

Table and figure captions

Figure 1 Flowchart illustrating the selection of BPD genetic studies

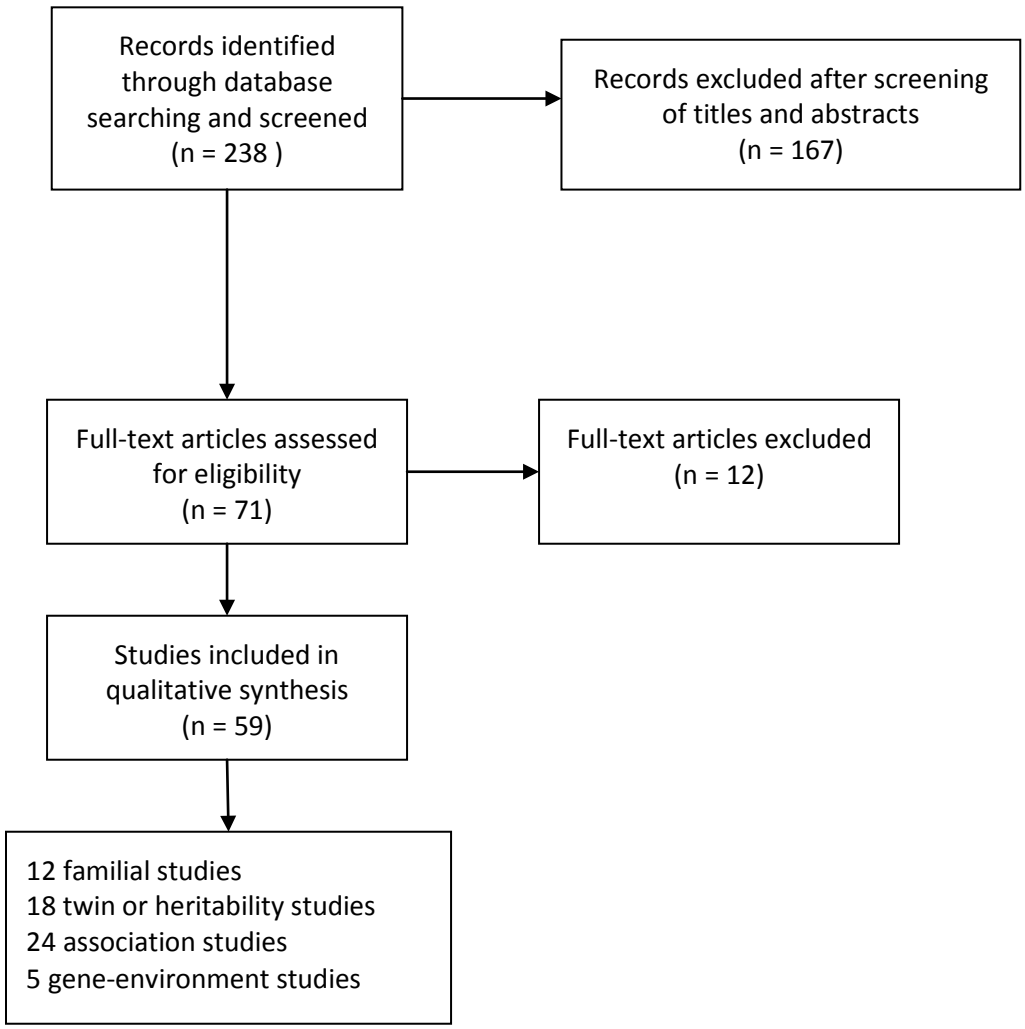
Figure 2 Hypothetical pathogenesis model for borderline personality disorder (BPD). A childhood environmental imbalance in favor of negative events may contribute to impulsivity and emotional dysregulation through interplay with plasticity genes. To reduce or avoid intense or negative affects, individuals develop maladaptive behaviors that may, in turn, be reinforced and repeated in the case of a predominantly negative environment. In this framework, BPD ultimately results from the conjunction of minimal behavioral flexibility and maximal repetitiveness. Before such an ultimate stage, the interaction between plasticity genes and a more "positive" environment may alter the personality trajectory and increase the risk of psychopathology in general (i.e., psychopathologies other than BPD) or lead to a lack of psychopathology.

Table 1 Genetic association studies on borderline personality disorder (BPD)

Table 2 Pooled odds ratios (ORs) for polymorphisms tested in two or more case-control studies

Table 3 Gene–environment studies in borderline personality disorder (BPD)

Box 1 Recommendations for future research regarding the genetics of BPD


Records identified through database searching and screened (n = 238)
Records excluded after screening of titles and abstracts (n = 167)
Full-text articles assessed for eligibility (n = 71)
Full-text articles excluded (n = 12)
Studies included in qualitative synthesis (n = 59)
12 familial studies
18 twin or heritability studies
24 association studies
5 gene-environment studies

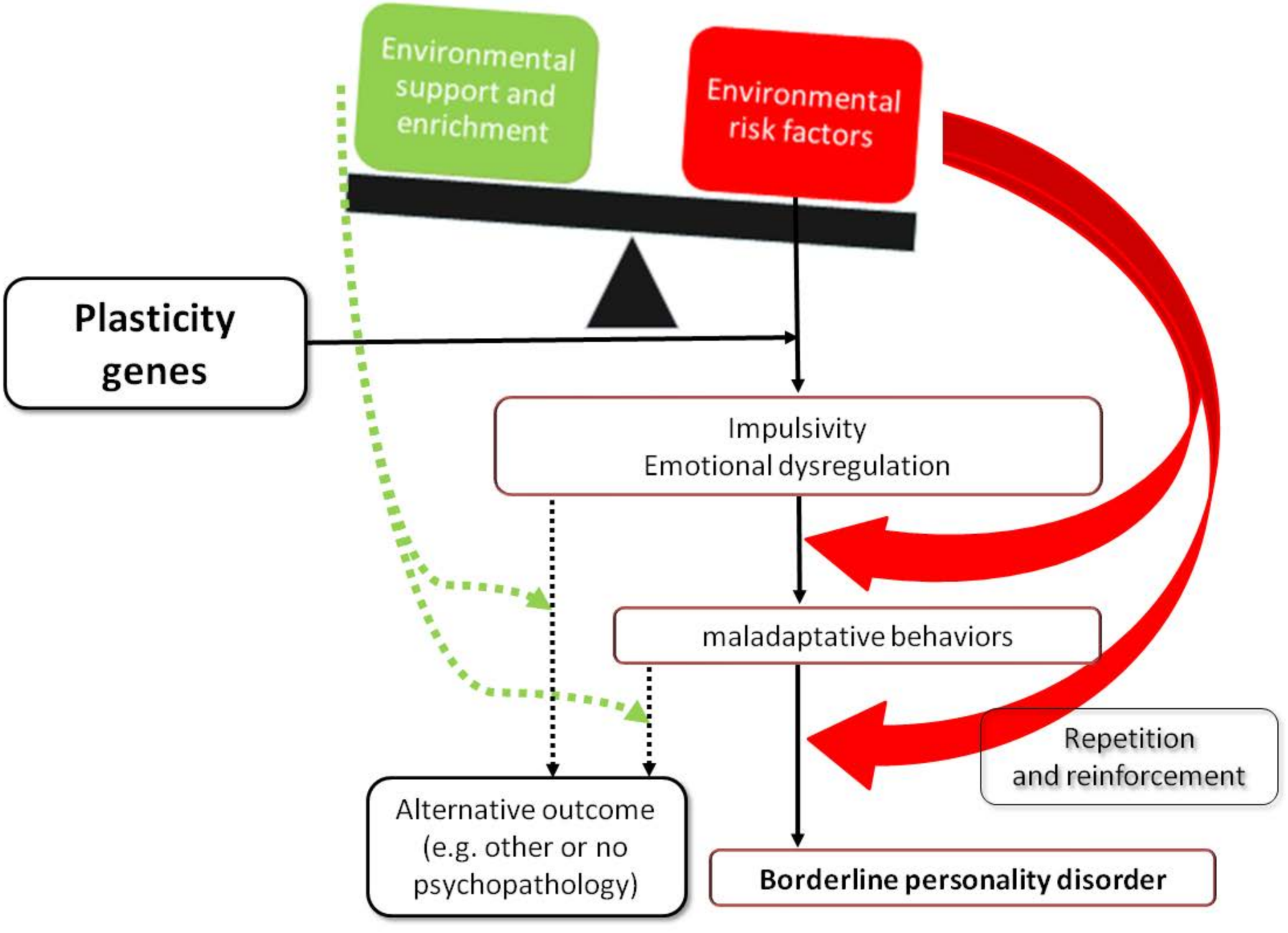

Environmental support and enrichment
Environmental risk factors
Plasticity genes
Impulsivity
Emotional dysregulation
maladaptative behaviors
Repetition and reinforcement
Alternative outcome (e.g. other or no psychopathology)
Borderline personality disorder

Table 1 Genetic association studies on borderline personality disorder (BPD)

Gene name	Gene symbol	Authors	Polymorphism investigated	Sample investigated	Type of analysis	Findings
Tryptophan hydroxylase 1	*TPH1*	Zaboli et al., 2006[a]	rs4537731, rs684302, rs211105, rs1800532, rs1799913, rs7933505	95 women with BPD/98 women controls	Case-control	Association with haplotype 'ACGCCG'
Tryptophan hydroxylase 1	*TPH1*	Maurex et al., 2009	ACGCCG haplotype	42 women with BPD, 30 controls	ANOVA	TPH1 haplotype association with BPD participants with impaired decision making
Tryptophan hydroxylase 1	*TPH1*	Wilson et al., 2009[a]	rs1800532	100 cases/101 controls	Case-control	Association with A allele
Tryptophan hydroxylase 1	*TPH1*	Wilson et al., 2012[a]	rs4537731, rs1800532	98 cases/300 depressed patients	Logistic regression	Association with A allele
Tryptophan hydroxylase 1	*TPH1*	Ni et al., 2009[a]	rs7130929, rs1800532	113 cases/113 controls	Case-control	No association
Tryptophan hydroxylase 2	*TPH2*	Perez-Rodriguez et al., 2010[*]	rs2171363, rs1386491, rs6582078, rs1352250 ("risk" haplotype)	109 cases/103 controls	Case-control	"Risk" haplotype was significantly more frequent in patients with BPD
Tryptophan hydroxylase 2	*TPH2*	Ni et al., 2009	rs4570625, rs11178997, rs10784941, rs1843809, rs1386494, rs2171363, rs1487280, rs1872824	113 cases/113 controls	Case-control	Association with rs2171363T
Serotonin receptor 1A	*HTR1A*	Ni et al., 2009	rs6295, rs878567, rs749099, rs1364043	113 cases/113 controls	Case-control	No association
Serotonin receptor 1A	*HTR1A*	Zetzsche et al., 2008	rs6295 G/C	25 women with BPD, 25 matched controls	Case-control coupling genetic/MRI	Patients with the 5-HTR1A G allele had significantly smaller amygdala volumes than those with the C/C genotype
Serotonin receptor 1B	*HTR1B*	Ni et al., 2009[b]	rs1213371, rs11568817, rs130058, rs6296, rs6297	113 cases/113 controls	Case-control	No association
Serotonin receptor 1B	*HTR1B*	Tadić et al., 2009[b]	rs11568817, rs130058, rs6296, rs6297	161 cases/156 controls	Case-control	No association
Serotonin receptor 1D	*HTR1D*	Ni et al., 2009	rs674386, rs6300, rs604030	113 cases/113 controls	Case-control	No association
Serotonin receptor 2A	*HTR2A*	Ni et al., 2006a	rs6313 (T102C), rs4941573, rs2296972, rs6314 (His452Tyr)	111 cases/287 controls	Case-control	Association with borderline personality traits
Serotonin receptor 5-HT2C	*HTR2C*	Ni et al., 2009	VNTR (201,207), rs6318	113 cases/113 controls	Case-control	Association with rs6318G
Serotonin receptor 5-HT3A	*HTR3A*	Ni et al., 2009	rs1062613, rs1176719, rs948983	113 cases/113 controls	Case-control	No association
Serotonin transporter	*5HTT*	Tadić et al., 2010[c]	HTTLPR: S/L, rs25531, STin2	156 cases/152 controls	Case-control	No association
Serotonin transporter	*5HTT*	Ni et al., 2006b[c]	HTTLPR: S/L, VNTR polymorphisms	89 cases/269 controls	Case-control	Association with 10-repeat VNTR

Serotonin transporter	*5HTT*	Pascual et al., 2007	HTTLPR: S/L, VNTR polymorphisms	65 patients with BPD	ANOVA	Patients with the L allele of the 5-HTTLPR polymorphism showed lower scores on the subscale of "liking parties and friends" of the Zuckerman-Kuhlman Personality Questionnaire. Patients with the 10-repeat VNTR polymorphism showed lower scores in "impulsivity", "sensation seeking" and on the subscale of "liking parties and friends"
Serotonin transporter	*5HTT*	Lyons-Ruth et al., 2007	5HTTLPR	96 young adults, 34 with BPD or APD features	Binary logistic regression models	The number of S alleles was significantly related to the incidence of BPD or APD traits
Serotonin transporter	*5HTT*	Pascual et al., 2008b[c]	5-HTTLPR and VNTR polymorphisms	86 cases/100 controls	Case-control	No association
Serotonin transporter	*5HTT*	Maurex et al., 2010	5-HTTLPR	77 women with BPD	Two-tailed t-test	Carriers of two S alleles of 5-HTTLPR reported more symptoms of borderline, suicidal, and self-injurious behavior
Serotonin transporter	*5HTT*	Tadic et al., 2009	5-HTTLPR	161 cases/156 controls	Case-control	No association
Serotonin transporter	*5HTT*	Silva et al., 2007	5-HTTLPR	59 patients with BPD	ANOVA	Carriers of the L-allele responded better to fluoxetine
Serotonin transporter	*5HTT*	Steiger et al., 2007*	5-HTTLPR	21 women with BPD from an initial sample of 90 women with bulimic syndromes	Logistic regression	Association
Monoamine oxidase A	*MAO*	Ni et al., 2007	promoter VNTR and an rs6323 T941G in exon 8	111 cases/289 controls	Case control	Association with VNTR
Dopamine transporter	*DAT1*	Joyce et al., 2006	9-repeat polymorphism	22 cases/135 depressed patients; 21 cases/157 depressed patients	Case control	Association with the 9-repeat allele of DAT1
Dopaminergic polymorphisms	*COMT, DAT1, DRD2, DRD4*	Nemoda et al., 2010	COMT rs4680, DAT1 40 bp VNTR, DRD2 TaqIB=rs1079597, TaqID=rs1800498, TaqIA=rs1800497, DRD4 48 bp VNTR	99 young adults and 136 patients with bipolar or major depressive disorder	Trait association	Association with the DRD2 TaqI B1-allele, A1-allele, and DRD4 -616 CC genotype
Tyrosine hydroxylase	*TH*	Tadić et al., 2010	TH Val81Met	156 cases/152 controls	Case-control	No association
Catechol-O-methyl transferase	*COMT*	Tadic et al., 2009	rs4680	161 cases/156 controls	Case-control	Association with COMT Met158Met
Brain-derived neurotrophic factor	*BDNF*	Tadić et al., 2009	rs6265	161 cases/156 controls	Case-control	No association
SCN9A	*SCN9A*	Tadić et al., 2008	rs16851799, rs7607967, rs4371369, rs4453709, rs4597545, rs4387806,	161 cases/156 controls	Case-control	No association

			rs6754031, rs12620053, rs13017637, rs12994338, rs4447616			
Arginine vasopressin receptor 1A gene	*AVR1A*	Vogel et al., 2012	microsatellite polymorphisms of the AVPR1A gene: AVR, RS1, RS3	161 cases/157 controls	Case-control	No association
Neurexin 3	*NRXN3*	Panagopoulos et al., 2013	23 SNP	Genotypic and borderline phenotypic data (borderline traits were available for 1439 heroin-dependent cases and 507 controls	Trait association	No association

[a] Studies used for the *TPH1* meta-analysis

[b] Studies used for the *HTR1B* meta-analysis

[c] Studies used for the 5-HTTLPR and 5-HTT VNTR meta-analysis

*Studies not included in the meta-analysis because the data provided were insufficient

Table 2: Pooled odds ratios (ORs) for polymorphisms tested in two or more case-control studies

Gene (variant)	Number of studies included	N (BPD patients/controls)	Pooled OR	95% CI	P value
5HTT/*SLC6A4* (5HTTLPR)	3	331/521	0.912	0.746 - 1.115	0.37
5HTT/SLC6A4 (STin2 VNTR)	3	331/521	1.216	0.824 - 1.795	0.32
HTR1B (rs6296)	2	274/269	1.045	0.794 - 1.375	0.75
HTR1B (rs6297)	2	274/269	1.236	0.882-1.733	0.21
HTR1B (rs130058)	2	274/269	0.890	0.685 - 1.156	0.38
HTR1B (rs11568817)	2	274/269	1.018	0.802 - 1.292	0.88
TPH1 (rs1800532)	4	406/612	0.995	0.829 - 1.193	0.95

Table 3 Gene–environment studies in borderline personality disorder (BPD)

Polymorphism investigated	Authors	Sample investigated	Type of analysis	Findings
SLC6A4 (5-HTTLPR)	Wagner et al., 2009	159 patients with BPD	ANOVA, regression analyses	SLEs[a] were associated with a decrease in impulsivity in SS/SL carriers.
COMT (rs4680)	Wagner et al., 2010	159 patients with BPD	Linear regression analyses	No modulating effects
BDNF (rs6265)	Wagner et al., 2010	159 patients with BPD	ANOVA, regression analyses	Childhood sexual abuse decreased impulsive aggression in BDNF Val/Val carriers
COMT (rs4680)	Wagner et al., 2010	112 women with BPD	ANOVA, regression analyses	In COMT Val158Val carriers, childhood sexual abuse and the number of SLE were associated with decreased impulsive aggression
TPH1 (rs4537731 and rs1800532)	Wilson et al., 2012	398 patients with mood disorders assessed for BPD and sexual abuse	Logistic regression	Significant interaction effects between genotype and abuse history

[a] SLE: serious life events

LA NEUROPLASTICITÉ ÂGE-DÉPENDANTE

I made a promise on the grave of my slain parents…

Bruce Wayne

3.1. Définition et hypothèse

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 and 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 *posttraumatic 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 (cf. **Article 1**) qu'il a été proposé que le TPB pourrait constituer une forme complexe de PTSD (Lewis and 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 hyperactivité limbique et une hypoactivité préfrontale en imagerie fonctionnelle (Shin et al., 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.

3.2. Partie expérimentale

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. Comme nous l'avons vu dans l'**Article 1**, les gènes impliqués dans la régulation de l'axe hypothalamo-hypophyso-adrénergique (HPA) (Cf. **Figure 3**), également appelé axe du stress, semblent être de très bons gènes candidats.

Le gène *FKBP5,* de 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-chaperone 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 and Binder, 2014). Nous présenterons ici les résultats préliminaires d'une étude génétique d'association du TPB, avec étude de réplication, sur les polymorphismes génétiques de FKBP5.

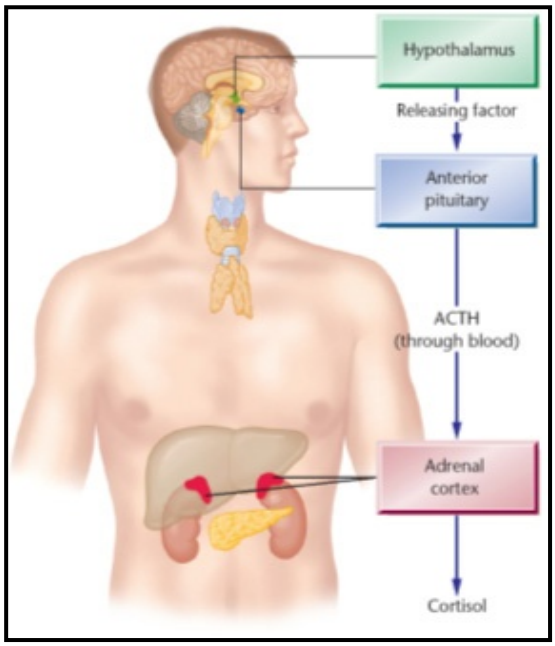


Figure 3: L'axe hypothalamo-hypophyso-adrénergique (noté HPA en anglais). L'hypothalamus synthétise le CRH (Cortisol Releasing Hormone) qui va stimuler la synthèse hypophysaire d'ACTH (adrenocorticotropic hormone) qui va agir au niveau périphérique pour stimuler la synthèse de glucocorticoïdes par les glandes surrénales.

3.2.1. Matériel et méthode

3.2.1.1. *Sujets*

Tous les sujets (patients et témoins) ont signés un consentement éclairé après avoir reçu une information claire et des explications complètes sur l'étude. L'étude a été approuvée par le Comité de Protection des Personnes de Lille (CPP Nord-Ouest IV, France).

106 patients caucasiens borderline âgés de plus de 18 ans (selon les critères du DSM-IV) ont été recrutés à partir du réseau de soins de psychiatrie lillois (moyenne d'âge : 34.4 ans +/- 10.4). 4 patients ont été exclus car ils ne répondaient pas aux critères diagnostics, 102 patients ont ainsi été retenus (86 femmes et 16 hommes). 135 témoins caucasiens sains majeurs (125 femmes et 10 hommes) ont également été recrutés (moyen d'âge : 23.8 ans +/- 6.9). À l'heure actuelle, seuls les résultats de 84 patients comparés à 111 témoins peuvent être présentés.

Le diagnostic de personnalité borderline a été déterminé grâce à la version française du *Structured Clinical Interview for DSM disorders II* (SCID II) (Bouvard et al., 1999). La recherche de différents types de maltraitance infantile a été réalisée grâce au *Childhood Trauma Questionnaire* (CTQ) (Bernstein et al., 1994).

3.2.1.2. *Critères d'inclusion et d'exclusion*

Ces critères sont résumés dans le **tableau 2**.

Au cours des visites d'évaluation clinique (questionnaires et échelles) un prélèvement salivaire de 2 ml, pour chaque sujet ayant accepté de participer à l'étude, a été réalisé. Ce prélèvement a permis une extraction d'ADN de haute qualité à partir des échantillons.

	Inclusion	Exclusion
Patients	- Accord pour participer à l'étude - Diagnostic validé : SCID II - Majeur > 18 ans	- Refus de participer à l'étude - Non validation diagnostique : SCID II - Mineur < 18 ans
Témoins	- Accord pour participer à l'étude - Non réponse aux critères diagnostiques de la pathologie PDQ4 < 5 - Majeur > 18 ans	- Refus de participer à l'étude - Réponse aux critères diagnostiques de la pathologie PDQ4 ≥ 5 - Mineur < 18 ans

Tableau 2 : Critères d'inclusion et de non inclusion des sujets.

3.2.1.3. *Échantillon de réplication*

Ce travail a été réalisé en collaboration avec l'hôpital de la Charité à Berlin où 124 patients souffrant de TPB et 95 témoins sains ont été recrutés. Pour l'échantillon de sujets allemands, dont nous ne présenterons qu'un résultat préliminaire, le diagnostic de TPB a été porté au moyen de la même échelle (SCID II).

3.2.1.4. *Sélection des SNP*

Les SNP (Single Nucleotide Polymorphism ou polymorphisme nucléotidique simple) sont des variations stables de la séquence d'ADN génomique, portant sur une seule base, qui existent environ toutes les 100 à 300 bases du génome et qui affectent au moins 1 p. 100 d'une certaine population. A ce jour plus de 2 millions de SNP ont été identifiés. La plupart des SNP se trouvent dans des régions non codantes et beaucoup de SNP n'ont pas d'implications fonctionnelles. Certains SNP se trouvant dans les régions codantes et dans les régions régulatrices des gènes peuvent participer à la prédisposition de maladies multifactorielles (Griffiths et al., 2002)**.** Nous pouvons à l'heure actuelle présenter les résultats pour le SNP rs737054.

3.2.1.5. *Génotypage et analyses statistiques*

Après extraction et quantification de l'ADN, Le génotypage de l'ADN des sujets est réalisé grâce à la PCR (*Polymerase Chain Reaction*) quantitative en temps réel à l'aide de la fluorescence grâce à la technique de génotypage des SNP Taqman ® (*Applied Biosystem*).

L'équilibre de Hardy-Weinberg (HW) a été vérifié pour grâce au logiciel Haploview pour l'ensemble des sujets. Ce logiciel permet également de réaliser un test d'association cas-témoins pour rechercher une association entre le TPB et un polymorphisme génétique. Il s'agit d'un test du chi-2 comparant la fréquence d'un polymorphisme chez les témoins à la fréquence du même polymorphisme chez les patients (TPB). Ce test a été réalisé pour tous les polymorphismes (SNP) sélectionnés.

3.2.2. Résultats

Nos résultats mettent en évidence une tendance à l'association entre le rs737054 du gène *FKBP5* et le TPB, avec une valeur de p égale à 0,08 dans l'échantillon français et une association statistiquement significative dans l'échantillon allemand (p = 0.01).

SNP	Allèle	Fréquence cas / contrôles	chi-2	Valeur p
rs737054	A	110:58 / 163:59	2.876	**0.08**

Tableau 3 : Résultats des tests d'association et fréquences alléliques des SNP testés dans l'échantillon français

SNP	Allèle	Fréquence cas / contrôles	chi-2	Valeur p
rs737054	A	186:56 / 142:72	6.207	**0.01**

Tableau 4 : Résultats des tests d'association et fréquences alléliques des SNP testés dans l'échantillon allemand

3.2.3. Conclusion et perspectives

Il s'agit de la première étude d'association entre le TPB dans une perspective d'analyse de marqueurs génétiques impliqués dans la régulation de l'axe HPA. Nos résultats ont mis en évidence une tendance à l'association entre le rs737054 du gène *FKBP5* et le TPB (p = 0,08) dans l'échantillon français et une association statistiquement significative dans l'échantillon allemand (p = 0.01). Il s'agit de résultats préliminaires et les analyses doivent se poursuivre pour : terminer le génotypage de tous les patients, rechercher une interaction gène-environnement, tester d'autres SNP de *FKBP5* et réaliser des analyses haplotypiques.

En considérant la NP âge-dépendante, nos résultats vont dans le sens d'une vulnérabilité génétique commune entre le TPB et le PTSD. En effet, des polymorphismes du gène *FKBP5* ont été associés au PTSD (Binder et al., 2008) et ces résultats ont de plus été répliqués plusieurs fois (pour revue voir (Zannas and Binder, 2014)). Le TPB pourrait donc résulter d'un traumatisme sur un cerveau en développement alors que le PTSD résulterait d'un trauma sur un cerveau adulte déjà développé. Le TPB et le PTSD constitueraient une seule et même entité : les « troubles liés aux trauma », dont la principale différence étiologique serait l'âge de survenue du traumatisme.

Les perspectives de ce travail, dont les résultats préliminaires sont exposés dans cette thèse, sont d'abord de tester d'autres SNP du gène *FKBP5*, et dans un deuxième temps de rechercher une interaction gène x environnement dans le développement du TPB.

LA NEUROPLASTICITÉ SYMPTÔME-DÉPENDANTE

If the doors of perception were cleansed everything would appear to man as it is, infinite.

William Blake

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.

4.1. L'hypothèse de la dysconnectivité de la schizophrénie

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). Bleuler, en prenant comme point de départ cette théorie, puis en s'en démarquant à cause des implications anatomiques du concept de Wernicke, va développer le concept psychopathologique de dissociation (Berrios et al., 2003).

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 fonctionnelle. Nous pouvons citer à titre d'exemple 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). En effet, selon Stephan (Stephan et al., 2006), le terme initial construit à partir du préfixe d'origine latine « dis » peut faire évoquer que la connectivité dans la schizophrénie est réduite, ce qui ne correspond pas à l'hypothèse de Friston. Pour éviter cette confusion, il est préférable de parler de dysconnectivité (traduction de l'anglais « *dysconnectivity* ») construit à partir du préfixe grec « dys » évoquant ainsi une connectivité anormale impliquant une intégration fonctionnelle anormale entre plusieurs régions cérébrales basée sur une plasticité synaptique anormale dans la schizophrénie, plutôt qu'une connectivité réduite.

L'hypothèse de la dysconnectivité dans la schizophrénie correspondrait 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.

Les travaux en faveur d'une dysconnectivité dans la schizophrénie sont nombreux, nous pouvons citer encore une fois à titre d'exemple les travaux de Friston et Frith en imagerie fonctionnelle montrant la connectivité fonctionnelle anormale entre les régions temporales et frontales (Friston et al., 1996). Les travaux d'électroencéphalographie (EEG), retrouvent également des arguments allant dans le même sens avec les travaux de Saito et al. indiquant une perte de coordination des régions cérébrales antérieures chez les patients schizophrènes (Saito et al., 1998) et les travaux de Ford et al. montrant une connectivité fonctionnelle fronto-temporale réduite chez des patients schizophrènes contribuant probablement à l'attribution externe (des voix) de pensées internes (Ford et al., 2002).

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 et al., 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 et al., 2009). On peut citer le gène codant pour la protéine Neuréguline 1. Ce gène noté NRG1, est impliqué dans la gliogenèse, la myélinisation au cours du développement et la NP. L'association de ce gène à la schizophrénie est solide puisqu'elle a été répliquée plusieurs fois (Munafo et al., 2006; Stefansson et al., 2002). Un autre gène, nommé DISC1, pour *Disrupted In Schizophrenia*, codant pour une protéine impliquée dans la migration neuronale, la NP et la neurogenèse, a également été associé à la schizophrénie (Ekelund et al., 2004; Hodgkinson et al., 2004). De façon plus spécifique, des associations ont été retrouvées entre DISC1 et certaines dimensions symptomatiques ou cliniques dans la schizophrénie. On retrouve notamment une association avec des troubles au niveau de la mémoire de travail, la mémoire à long terme, un volume de l'hippocampe faible (Callicott et al., 2005; Cannon et al., 2005). Ces observations suggèrent que les effets de DISC1 sur la vulnérabilité à la schizophrénie pourraient impliquer un dysfonctionnement de l'hippocampe.

Récemment une preuve considérable de la dysconnectivité, impliquant des gènes associés au développement cérébral et à la mise en place de connexions synaptiques, a été apportée. Des cellules de la peau (fibroblastes) de 4 patients souffrant de schizophrénie ont d'abord été prélevées puis transformées en cellules souches pluripotentes, et finalement en neurones. Des neurones à partir de témoins non schizophrènes ont été réalisés de la même manière. Après mise en culture, les neurones produits à partir des patients diffèrent de ceux issus des témoins. Les connexions entre les neurones issus des patients schizophrènes présentent une connectivité moindre par rapport à celles des témoins. Les analyses génétiques ont permis d'identifier 600 gènes dérégulés dans ces neurones, dont 25% avaient déjà été impliqués dans la schizophrénie antérieurement. Enfin, les paramètres (expression génétique et connectivité) tendent à s'approcher des profils des témoins quand un traitement antipsychotique est testé *in vitro* (Brennand et al., 2011).

Ces anomalies génétique constitutives peuvent tout à fait interagir avec des facteurs environnementaux dans une hypothèse d'interaction gène-environnement (Stephan et al., 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 et al., 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 and Poo, 2001). C'est cette force de connexion entre deux neurones qui va déterminer si leur connexion va survivre à « l'élagage développemental » (Hua and Smith, 2004).

4.2. Dysconnectivité et hallucinations

L'hypothèse de la dysconnectivité peut s'appliquer à des symptômes spécifiques comme les hallucinations (**Article 2**). 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 (**Article 3**). L'approche dimensionnelle permet l'étude des dimensions symptomatiques de la schizophrénie dans le but de réduire l'hétérogénéité clinique de la maladie. Elle permet notamment de développer une approche quantitative allant du normal au pathologique, de travailler sur des dimensions plus élémentaires et enfin de développer des approches transnosographiques. La dimension hallucinatoire apparaît alors comme une dimension symptomatique de choix.

Après un court rappel clinique sur les hallucinations dans la schizophrénie nous exposerons nos travaux sur l'étude de la dysconnectivité en imagerie cérébrale dans un symptôme précis : les hallucinations visuelles.

Le mot hallucination provient du latin *hallucinatio* qui signifie erreur, méprise, égarement. L'hallucination est classiquement définie depuis Ball (1833-1893) comme une perception sans objet. Baillarger (1809-1890) va permettre grâce à ses descriptions sémiologiques de distinguer les hallucinations psychosensorielles (perception par les organes des sens) des hallucinations intrapsychiques (les patients perçoivent leurs propres pensées sans intervention des organes sensoriels).

Dans la schizophrénie, un sujet sur deux rapporte des hallucinations psychosensorielles (Cutting and Dunne, 1989). Les hallucinations les plus fréquentes sont les hallucinations auditives présentes chez environ 60 à 70 % des patients (Andreasen and Flaum, 1991). Il peut s'agir de sons simples (sonnerie, mélodie), mais le plus souvent il s'agit de voix nettement localisées dans l'espace, on parle alors d'hallucinations acoustico-verbales. Il peut y avoir une ou plusieurs voix qui s'adressent au patient à la deuxième ou à la troisième personne, voire même qui conversent entre elles. La voix peut être celle d'un homme ou d'une femme, le sexe en général étant identifié par le patient. La voix peut être celle d'une personne connue ou non. La ou les voix expriment souvent des phrases courtes à connotation négative, voire des insultes, elles peuvent répéter les pensées du sujet (écho de la pensée), ou décrire ce que le sujet fait (commentaire des actes). Les hallucinations visuelles touchent quant à elles 15 % des patients schizophrènes et jusqu'à 70 % chez les patients présentant une schizophrénie chronique (Bracha et al., 1989). On peut retrouver des images simples comme des phosphènes, des ombres, ou beaucoup plus complexes comme un phœnix volant dans le ciel, ou de façon plus angoissante, des démons et des morts sortant du sol...

Les hallucinations tactiles sont présentes chez environ 5 % des patients schizophrènes (Cutting, 1990). Elles concernent la sensibilité externe (le toucher) des malades qui peuvent sentir un coup de vent sur le visage ou des frôlements, des sensations de brûlures, de piqûres, ou des mouvements de reptation sous la peau, appelé syndrome d'Ekbom du nom du psychiatre suédois qui a décrit cette dernière entité (Le Roux et al., 2004).

Les hallucinations touchant les autres sens sont plus rares, mais comme toutes les modalités sensorielles peuvent être touchées, on peut décrire les hallucinations olfactives (bonnes ou mauvaises odeurs) et gustatives, et les hallucinations cénesthésiques intéressant la sensibilité interne. Certains patients rapportent à ce sujet des sensations de transformation corporelle par exemple en diable ou en démon, ou encore des « hallucinations génitales » avec des sensations d'attouchements voire de viols.

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. Il a été montré que la connectivité fonctionnelle, basée sur les corrélations temporelles entre le signal BOLD (*Blood Oxygen Level Dependant*) de différentes régions cérébrales, est modifiée dans les aires du langage de patients souffrant de schizophrénie présentant des hallucinations auditives en comparaison à des contrôles (Allen et al., 2012). Des études de connectivité structurale, en imagerie en tenseur de diffusion (DTI), ont quant à elles montré des différences de connectivité, au niveau des aires du langage, en comparant des patients souffrant de schizophrénie hallucinés, non-hallucinés et des sujets sains non schizophrènes (Hubl et al., 2004). Il a ainsi été montré que des connexions aberrantes retrouvées dans les hallucinations acoustico-verbales (HAV) devenaient plus « fortes » chez les patients ayant d'avantage d'hallucinations et dont l'histoire de la maladie était plus longue (Rotarska-Jagiela et al., 2009).

Les travaux suivants (**Articles 4 et 5**), utilisant des 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 verrons ensuite 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 (**Article 6**). La morphologie corticale et la connectivité cérébrale sont effectivement étroitement liées.

En effet, Van Essen (Van Essen, 1997) fait l'hypothèse que la formation des circonvolutions cérébrales pourrait résulter de l'application des forces de traction interne exercées par les fibres nerveuses sur le cortex lors de la mise en place des connexions cérébrales *in utero.* Ainsi, si deux régions voisines sont très connectées au sein de la substance blanche, il en résulterait un rapprochement des deux régions ce qui conduirait au développement des gyri. Les sillons se formeraient, quant à eux, entre des régions moins connectées (White et al., 2010) (Cf. **Figure 4**).

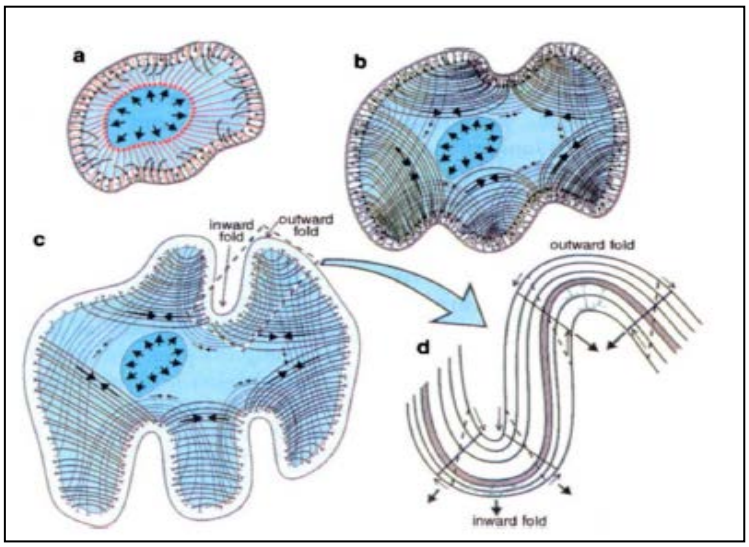


Figure 4: Modèle de Van Essen **(Van Essen, 1997)**. La mise en place des gyri et des sillons résulterait de phénomènes mécaniques de traction liés à des différences de densité de connexions régionales. a) Durant le développement précoce, les neurones (en noir) migrent le long des cellules gliales radiales (en rouge) b) la plupart des axones atteignent leurs structures cibles avant le début de la mise en place des plissements corticaux et des tensions entre ces axones (flèches), rapprochent les régions fortement interconnectées. c) Ce mécanisme induit alors deux types de plissement ceux dirigés vers l'extérieur, (régions fortement connectées), et ceux dirigés vers l'intérieur (régions faiblement connectées). d) Des forces compensatrices (petites flèches) tendent à épaissir les couches profondes le long des plis dirigés vers l'extérieur, et à amincir les couches superficielles le long des plis dirigés vers l'intérieur.

ARTICLE 2

Génétique des hallucinations: des voix pas sans gène !

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Génétique des hallucinations:

des voix pas sans gène !

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RÉSUMÉ

La schizophrénie est une maladie psychiatrique hétérogène, à hérédité complexe ayant des facteurs de risque génétiques et environnementaux. L'identification des facteurs génétiques est difficile, et se focaliser sur la dimension hallucinatoire peut permettre de réduire l'hétérogénéité phénotypique de la maladie. Les études génétiques, peu nombreuses concernant cette dimension clinique, s'intègrent dans différents modèles d'étude des hallucinations qui prennent en compte le rôle de concepts variés, allant des émotions à la dopamine (hypothèse dopaminergique) en passant par l'implication du langage. Le transporteur de la sérotonine (*5-HTT*), le gène codant pour le récepteur de cholecystokinine (*CCK-AR*) et le gène *FOXP2* (impliqué dans le langage), pourraient être impliqués dans les phénomènes hallucinatoires. Cette synthèse de la littérature nous invite à considérer que les futures études de génétique devraient se porter sur des populations caractérisées plus finement au niveau clinique (intensité, fréquence, modalité hallucinatoire…), et devraient s'intégrer dans un cadre théorique comme celui de la dysconnectivité et de la neuroplasticité. Cette approche est possible par le couplage de méthodes de génétique et d'imagerie, et permet de s'inscrire dans une compréhension plus globale de ce phénomène, à condition que les conditions nécessaires à ces recherches soient respectées, c'est-à-dire la collection de larges échantillons multicentriques utilisant les mêmes paradigmes.

I. Génétique de la schizophrénie : vers une approche dimensionnelle

La schizophrénie est une maladie psychiatrique complexe dont l'étiopathogénie, pour l'essentiel mal connue, implique clairement des facteurs génétiques. Il est bien démontré que l'héritabilité du trouble (voir **Glossaire**), calculée à partir d'études de jumeaux, est élevée, et estimée aux environs de 80 % [1]. Cependant, la nature de ces facteurs génétiques et leur mode de transmission restent méconnus et les résultats sont difficiles à appréhender malgré les progrès réalisés en biologie moléculaire et en épidémiologie génétique. Ainsi, aucune des 3 grandes études d'association pangénomiques (voir **Glossaire**) comparant des milliers de marqueurs génétiques (notamment des polymorphismes nucléotidiques simples, voir **Glossaire)** chez des milliers de sujets (selon un modèle cas-témoin) n'ont retrouvé de gène précédemment incriminé et régulièrement associé à la schizophrénie comme le gène de la Catechol-O-Methyltransferase (*COMT*) ou encore le gène Disrupted In Schizophrenia *DISC-1* [2–4]. Ainsi, les données les plus récentes conduisent à faire l'hypothèse d'un modèle étiopathogénique polygénique multifactoriel se traduisant par l'implication de combinaisons de variations génétiques rares et fréquentes, d'interaction entre les gènes (épistasie, voir **Glossaire**) et d'interactions entre les facteurs génétiques et environnementaux (interaction GxE) [5,6].

En plus de cette complexité génétique, il semble que les phénotypes issus des classifications internationales (CIM-10 et DSM-IV) manquent de pertinence pour les études génétiques de la schizophrénie [7]. Cette complexité de la relation entre le phénotype et le génotype dans les maladies psychiatriques a stimulé le développement d'outils de caractérisation phénotypique plus fins (*endo*phénotypiques) 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 et ainsi faciliter l'approche génétique [8]. Elle permet notamment de développer une approche quantitative allant du normal au pathologique, de

travailler sur des dimensions plus élémentaires [9] et enfin de développer des approches transnosographiques [10]. La dimension hallucinatoire apparaît alors comme une dimension symptomatique prometteuse et présente déjà quelques résultats encourageants [11].

II. Revue de littérature de la génétique des hallucinations

La plupart de ces études se sont centrées sur les troubles neurologiques associés à un risque plus élevé d'hallucinations (épilepsie, maladie d'Alzheimer, maladie de Parkinson) et les consommations de drogues ayant un potentiel psychodysleptique (cannabis, alcool). Il n'existe pas à notre connaissance d'études en population non clinique, malgré la fréquence de ce symptôme en population générale [12]. Finalement, il existe peu d'études de génétique des hallucinations dans la schizophrénie. Plusieurs facteurs peuvent expliquer ce faible nombre d'études comme la prédominance de l'approche catégorielle des maladies psychiatriques, et la trop grande hétérogénéité de ce phénotype [13].

Cependant, il existe des arguments forts en faveur de l'implication de facteurs génétiques dans les hallucinations. Ainsi, l'héritabilité de la dimension hallucinatoire dans la schizophrénie a récemment été estimée entre 33 et 43 % [14,15]. De plus, plusieurs gènes ont été associés aux hallucinations acoustico-verbales (HAV) dans la schizophrénie. Ces analyses génétiques se sont appuyées sur différents modèles théoriques des hallucinations dont ceux impliquant le rôle des émotions, de l'hypothèse dopaminergique et du langage.

II.1 Le rôle des émotions dans les HAV et le système sérotoninergique

L'émotion est un aspect essentiel de la perception et joue un rôle majeur dans le phénomène hallucinatoire chez les patients souffrant de schizophrénie [16]. D'un point de vue clinique, la ou les voix peuvent être décrits comme répétant les pensées du sujet (écho de la pensée), ou décrire ce que le sujet fait (commentaire des actes) [17]. Il s'agit plutôt de phrases courtes prenant souvent une connotation négative. Les insultes, notamment à caractère sexuel, sont fréquentes. Cet aspect sémiologique permet aisément de comprendre que chez les patients

souffrant de schizophrénie, les HAV impliquent un contenu émotionnel intense, pouvant être corrélé à l'état émotionnel général (faible estime de soi, éléments dépressifs) [18].

Les gènes impliqués dans le système sérotoninergique ont particulièrement été étudiés dans ce cadre. En effet, la sérotonine est un neurotransmetteur majeur dans la régulation des émotions. Le gène du transporteur de la sérotonine (*5-HTT*) a été étudié à cause de son rôle de régulation dans la disponibilité de sérotonine, il régule la concentration de sérotonine disponible dans la synapse en recaptant la sérotonine libre [19].

Un polymorphisme fonctionnel de la région promotrice du gène a été identifié (5HTTLPR). L'allèle court (S) est associé à une expression réduite du gène et à une diminution de la capture de sérotonine, l'allèle long (L) étant beaucoup plus actif sur le plan transcriptionnel. Une faible activité de recapture (génotype SS) entraîne une réduction de la transmission sérotoninergique par des phénomènes de désensibilisation [19]. L'allèle de faible expression du 5-HTTLPR (S) est considéré comme un facteur de risque génétique pour le développement de troubles psychiatriques, notamment de l'humeur et anxieux, en lien avec une majoration de la sensibilité au stress, à l'environnement, et à la psychopathologie [20]. Les variations de l'expression du *5-HTT* influençant la réactivité de l'organisme à l'exposition aux stress environnementaux augmentant le risque de dépression, il a été proposé que les variations d'expression de ce gène régulent la réponse émotionnelle aux HAV. Cette approche considère les HAV comme un événement stressant pour les patients et la réponse aux HAV d'un patient peut donc être modulée par son patrimoine génétique.

La première étude moléculaire du phénomène hallucinatoire est une étude d'association avec le polymorphisme fonctionnel du *5-HTT* [21]. Cette étude retrouve une association entre l'allèle L et l'intensité des HAV mais l'aspect émotionnel n'a pas été interrogé. Plus récemment, l'allèle S du transporteur de la sérotonine, a été montré associé à une réponse émotionnelle majorée aux HAV [22], ainsi qu'à un sentiment de détresse plus intense [23] chez des patients atteints de schizophrénie. L'étude du *5-HTT* a également été couplée à une approche en IRM fonctionnelle

(IRMf). Le protocole expérimental de cette étude consistait à faire écouter des mots chargés émotionnellement (fréquemment retrouvés dans les HAV) à des patients atteints de schizophrénie dans l'IRM. Il a été montré que l'activation de l'amygdale pendant l'écoute des mots chargés émotionnellement (aire cérébrale impliquée dans la régulation des émotions) était activée de façon plus intense chez les porteurs des génotypes SS en comparaison aux génotypes SL et LL [24].

II.2 L'hypothèse dopaminergique des hallucinations

C'est à partir de la découverte des neuroleptiques et de l'étude de leur cible pharmacologique : les récepteurs dopaminergiques, que Carlsson a formulé pour la première fois l'hypothèse dopaminergique de la schizophrénie [25]. Cette hypothèse propose que les signes positifs de la schizophrénie (le délire et les hallucinations) soient liés à une hyperactivation de la transmission dopaminergique au niveau mésolimbique. C'est dans ce cadre que les gènes impliqués dans la régulation du système dopaminergique ont été étudiés dans les hallucinations.

Le gène *DAT1* présente un polymorphisme, de type VNTR (voir **Glossaire**), qui modifie son expression. Dans une étude chez 178 patients schizophrènes une association a été trouvée associée entre l'allèle *DAT**10 et la sévérité et la fréquence des hallucinations, cependant ce résultat n'était pas significatif après correction statistique [26].

La cholecystokinine est un peptide cérébral impliqué dans la physiopathologie de la schizophrénie à travers son action médiatrice du relargage dopaminergique au niveau central [27]. Il existe deux types de récepteur les CCK-AR et CCK-BR respectivement codés par les gènes *CCK-AR* et *CCK-BR*. Plusieurs études ont souligné le rôle du gène *CCK-AR* dans les troubles psychiatriques sévères, il a ainsi été étudié dans le cadre des hallucinations. Wei et collaborateurs ont mis en évidence une association significative entre un polymorphisme du gène *CCK-AR* et les HAV dans une population de 210 patients atteints de schizophrénie [28]. Plusieurs études de réplication ont été réalisées et ont permis de confirmer ces résultats dans les HAV "épisodiques" [29] mais aussi dans les

HAV persistantes [30,31]. Ces résultats n'ont cependant pas été répliqués dans une étude réalisée en population chinoise [32].

Enfin, les polymorphismes des gènes *DRD2* et *DRD3* (codant pour des récepteurs dopaminergiques) ont été beaucoup étudiés dans la schizophrénie mais jamais spécifiquement dans les hallucinations.

II.3 Implication du langage dans les hallucinations: le gène FOXP2

Les HAV ont fait l'objet de nombreuses études scientifiques qui ont mis en évidence le rôle des aires de production et de réception du langage. Par exemple, une méta-analyse récente d'études d'imagerie fonctionnelle réalisées pendant les HAV a permis de mettre en évidence des activations dans les aires cérébrales de perception et de production de langage [33].

D'un point de vue théorique, il a été proposé que les HAV puissent être considérées comme un langage produit intérieurement par le sujet mais non reconnu par celui-ci comme autoproduit [34]. Il en résulterait une attribution erronée de pensées auto-générées à une source externe. De nombreux travaux ont permis de corréler l'implication du langage dans les hallucinations avec des anomalies cérébrales comme l'asymétrie anatomique cérébrale dans la schizophrénie ou encore le défaut de latéralisation [35]. Ainsi, les gènes impliqués dans le langage ont également été considérés comme gènes candidats dans le champ de l'étude des HAV.

Le gène *FOXP2,* premier gène à avoir été directement lié au langage, a particulièrement été étudié dans ce but. Le gène *FOXP2*, a été identifié dans une famille où les trois générations souffraient de troubles du langage [36]. Le gène *FOXP2* de la famille FOX code pour un facteur de transcription permettant de réguler l'expression de plusieurs autres gènes en se fixant directement sur l'ADN [37]. Plusieurs études d'association ont mis en évidence une association entre des polymorphismes de *FOXP2* et les HAV dans des populations de patients atteints de schizophrénie [38,39].

III. Hallucinations et neuroplasticité

Au-delà de son implication dans le langage, *FOXP2* est également impliqué dans les phénomènes de neuroplasticité (pour revue voir [40]), la neuroplasticité correspondant à la capacité du système nerveux à s'adapter aux changements environnementaux internes et externes. De plus, les hallucinations ne se limitent pas aux HAV dans la schizophrénie. Même si celles-ci sont plus fréquentes (60-80 %[41]), les hallucinations visuelles toucheraient quant à elles entre 24 et 72 % [42,43] des patients atteints de schizophrénie. De façon intéressante, des auteurs comme Ralf-Peter Behrendt font l'hypothèse de mécanismes physiopathologiques différents entre les patients présentant des hallucinations visuelles et auditives, qui seraient liées dans ce cas à une hyperactivité hippocampique. A l'inverse, chez les patients présentant uniquement des hallucinations auditives, le trouble pourrait être d'avantage lié à une dérégulation thalamo-corticale [44]. L'hypothèse de la dysconnectivité de la schizophrénie représente une des théories les plus prometteuses à l'heure actuelle qui pourrait permettre de dépasser cette complexité biologique et clinique.

La dysconnectivité dans la schizophrénie correspondrait à une connectivité défectueuse entre les différentes aires cérébrales se manifestant par une intégration fonctionnelle anormale des systèmes neuronaux spécialisés (population de neurones, aires corticales…) indispensables aux processus sensorimoteurs et cognitifs. Cette connectivité défectueuse serait associée à un contrôle défectueux de la plasticité synaptique [45–47]. Différents mécanismes explicatifs de cette dysconnectivité ont été proposés. Ils impliqueraient des facteurs génétiques [48,49] et environnementaux [50] entrainant une altération de la mise en place des connexions anatomiques au cours du développement ainsi que des anomalies de la plasticité et de la transmission synaptique [46]. Ces anomalies génétiques constitutives peuvent tout à fait interagir avec des facteurs environnementaux dans une hypothèse d'interaction gène-environnement [47], où des anomalies génétiques entraineraient un défaut au niveau architectural (génétique), auto-entretenu ou facilité

par des mécanismes neuroplastiques « expérience dépendant » liés à l'influence de l'environnement (interne ou externe) [46]. Ainsi, la connexion entre deux neurones est fonction de la plasticité synaptique dite « expérience-dépendante » et se trouve d'autant plus renforcée qu'elle est utilisée [51]. C'est cette force de connexion entre deux neurones qui va déterminer si leur connexion va survivre à « l'élagage développemental » [52].

L'hypothèse de la dysconnectivité peut s'appliquer à des symptômes spécifiques comme les hallucinations [53]. Des arguments en faveur du concept de dysconnectivité chez des patients atteints de schizophrénie présentant des hallucinations auditives ont été apportés par différentes méthodes d'imagerie [54]. Il a ainsi été montré que des connexions aberrantes retrouvées dans les HAV devenaient plus « fortes » chez les patients ayant d'avantage d'hallucinations et dont l'histoire de la maladie était plus longue [55]. Ainsi, l'hypothèse de la dysconnectivité et son approche neuroplastique pourrait permettre une compréhension générale du rôle des gènes et neurotransmetteurs identifiés dans les hallucinations. Par exemple, les gènes, mis en évidence dans les HAV, pourraient être considérés comme des "gènes de plasticité", entrainant chez les patients une plus grande susceptibilité à l'influence de l'environnement (interne ou externe), plutôt que simplement comme des "gènes de vulnérabilité" [56].

IV. Conclusion et perspectives

Cette revue de littérature portant sur la génétique des hallucinations a permis une synthèse de premiers résultats encourageants dans le domaine. Le transporteur de la sérotonine (*5-HTT*), le gène codant pour le récepteur de cholecystokinine (*CCK-AR*) et le gène *FOXP2* impliqué dans le langage, semblent tous présenter un rôle dans les phénomènes hallucinatoires. Plusieurs axes de recherche sont à développer, notamment grâce à l'utilisation d'outils cliniques permettant de mieux caractériser le phénomène hallucinatoire. Il semble par exemple que la physiopathologie des hallucinations dans la schizophrénie puisse être différente selon la ou les modalités sensorielles engagées. Les études de génétique devraient alors se porter sur des échantillons de patients mieux caractérisés au niveau clinique (intensité, fréquence, modalité…), et pourraient s'intégrer dans un cadre théorique plus global comme la dysconnectivité et son approche neuroplastique. Ces stratégies notamment pourraient permettre d'optimiser le couplage entre méthodes de génétique et d'imagerie afin de fournir une compréhension plus intégrée des hallucinations.

Glossaire

Épistasie: interaction entre plusieurs gènes.

Étude d'association: étude qui consiste à rechercher une association entre une maladie et un nombre limité de polymorphismes localisés sur un gène dit "candidat" en comparant les fréquences alléliques de ces polymorphismes entre une population de patients et une population de témoins sains (ou sujets contrôles).

Études d'association pangénomique (en anglais, Genome Wide Association Study, GWAS): étude d'association analysant des centaines de milliers de polymorphismes génétiques en utilisant des techniques de génotypage à haut débit. Il s'agit d'outils très utilisés pour l'analyse des maladies multifactorielles telle la schizophrénie. Il n'y a pas d'hypothèse préalable sur les gènes d'intérêt contrairement aux études d'association génétique de type gène candidat.

Héritabilité: pourcentage d'explication de la maladie par la génétique. Autrement dit, il s'agit de la part de variance phénotypique expliquée par les facteurs génétiques.

Polymorphismes Nucléotidiques Simples (en anglais, Single Nucleotid Polymorphism, SNP): polymorphismes binaires de la séquence d'ADN portant sur un seul nucléotide.

VNTR (Variable Numbers of Tandem Repeats) ou mini-satellites: motifs répétées en tandem, de 10 à 50 paires de bases.

RÉFÉRENCES

1. van Os J, Kapur S. Schizophrenia. The Lancet. 2009 22;374(9690):635–45.

2. Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature. 2009 6;460(7256):753–7.

3. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, et al. Common variants conferring risk of schizophrenia. Nature. 2009 6;460(7256):744–7.

4. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009 6;460(7256):748–52.

5. Keshavan MS, Nasrallah HA, Tandon R. Schizophrenia, « Just the Facts » 6. Moving ahead with the schizophrenia concept: From the elephant to the mouse. Schizophrenia Research. 2011;127(1–3):3–13.

6. Gejman PV, Sanders AR, Kendler KS. Genetics of Schizophrenia: New Findings and Challenges. Annual Review of Genomics and Human Genetics. 2011;12(1):121–44.

7. Krebs M-O, Joober R. Génétique de la schizophrénie : le grand retour vers la clinique ? L'Encéphale. 2010;36(2):91–3.

8. Boks MPM, Leask S, Vermunt JK, Kahn RS. The structure of psychosis revisited: The role of mood symptoms. Schizophrenia Research. 2007;93(1–3):178–85.

9. Schürhoff F. Déterminants génétiques des idées délirantes. Annales Médico-psychologiques, revue psychiatrique. 2011;169(3):175–8.

10. Bellivier F, Geoffroy P, Scott J, Schurhoff F, Leboyer M, Etain B. Biomarkers of bipolar disorder: specific or shared with schizophrenia? Frontiers in Biosciences. in press;

11. Sanjuan J, Aguilar EJ, Frutos R de. Time for a broad phenotype in schizophrenia? BJP. 2006 2;188(2):190–190.

12. Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. Schizophrenia Research. 2002 1;54(1-2):59–65.

13. Preston GA, Weinberger DR. Intermediate phenotypes in schizophrenia: a selective review. Dialogues in Clinical Neuroscience. 2005;7(2):165.

14. McGrath JA, Avramopoulos D, Lasseter VK, Wolyniec PS, Fallin MD, Liang K-Y, et al. Familiality of novel factorial dimensions of schizophrenia. Arch. Gen. Psychiatry. 2009;66(6):591–600.

15. Hur Y-M, Cherny SS, Sham PC. Heritability of hallucinations in adolescent twins. Psychiatry Research. (0).

16. Cohen AS, Minor KS. Emotional Experience in Patients With Schizophrenia Revisited: Meta-analysis of Laboratory Studies. Schizophrenia Bulletin. 2008 17;36(1):143–50.

17. Amad A, Bubrovszky M, Maître E, Thomas P. Schizophrénie de l'adulte. Pathologies schizophréniques. Médecine Sciences. 2012. p. 96–110.

18. Smith B, Fowler DG, Freeman D, Bebbington P, Bashforth H, Garety P, et al. Emotion and psychosis: Links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. Schizophrenia Research. 2006;86(1–3):181–8.

19. Heils A, Teufel A, Petri S, Stöber G, Riederer P, Bengel D, et al. Allelic Variation of Human Serotonin Transporter Gene Expression. Journal of Neurochemistry. 1996;66(6):2621–4.

20. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic Sensitivity to the Environment: The Case of the Serotonin Transporter Gene and Its Implications for Studying Complex Diseases and Traits. American Journal of Psychiatry. 2010 15;167(5):509–27.

21. Malhotra AK, Goldman D, Mazzanti C, Clifton A, Breier A, Pickar D. A functional serotonin transporter (5-HTT) polymorphism is associated with psychosis in neuroleptic-free schizophrenics. Molecular Psychiatry. 1998 4;3(4):328–32.

22. Sanjuan J, Rivero O, Aguilar EJ, González JC, Moltó MD, de Frutos R, et al. Serotonin transporter gene polymorphism (5-HTTLPR) and emotional response to auditory hallucinations in schizophrenia. Int. J. Neuropsychopharmacol. 2006;9(1):131–3.

23. Rivero O, Sanjuan J, Aguilar EJ, Gonzalez JC, Molto MD, de Frutos R, et al. Serotonin transporter gene polymorphisms and auditory hallucinations in psychosis. Rev Neurol. 2010 16;50(6):325–32.

24. Aguilar EJ, Sanjuan J, García-Martí G, Lull JJ, Robles M. MR and genetics in schizophrenia: Focus on auditory hallucinations. European Journal of Radiology. 2008;67(3):434–9.

25. Carlsson A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology. 1988;1(3):179–86.

26. Georgieva L, Dimitrova A, Nikolov I, Koleva S, Tsvetkova R, Owen MJ, et al. Dopamine transporter gene (DAT1) VNTR polymorphism in major psychiatric disorders: family-based association study in the Bulgarian population. Acta Psychiatrica Scandinavica. 2002;105(5):396–9.

27. Seutin V. Dopaminergic neurones: much more than dopamine? British Journal of Pharmacology. 2005;146(2):167–9.

28. Wei J, Hemmings G. The CCK-A receptor gene possibly associated with auditory hallucinations in schizophrenia. European Psychiatry. 1999;14(2):67–70.

29. Tachikawa H, Harada S, Kawanishi Y, Okubo T, Suzuki T. Linked polymorphisms (–333G>T and –286A>G) in the promoter region of the CCK-A receptor gene may be associated with schizophrenia. Psychiatry Research. 2001 20;103(2–3):147–55.

30. Sanjuan J, Toirac I, González JC, Leal C, Moltó MD, Nájera C, et al. A possible association between the CCK-AR gene and persistent auditory hallucinations in schizophrenia. European Psychiatry. 2004;19(6):349–53.

31. Toirac I, Sanjuán J, Aguilar EJ, González JC, Artigas F, Rivero O, et al. Association between CCK-AR gene and schizophrenia with auditory hallucinations. Psychiatr. Genet. 2007;17(2):47–53.

32. Zhang XY, Zhou DF, Zhang PY, Wei J. The CCK-A receptor gene possibly associated with positive symptoms of schizophrenia. Mol. Psychiatry. 2000;5(3):239–40.

33. Jardri R, Pouchet A, Pins D, Thomas P. Cortical Activations During Auditory Verbal Hallucinations in Schizophrenia: A Coordinate-Based Meta-Analysis. Am J Psychiatry. 2011 1;168(1):73–81.

34. Frith CD. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. Psychol Med. 1987;17(3):631–48.

35. Sommer I, Ramsey N, Kahn R, Aleman A, Bouma A. Handedness, language lateralisation and anatomical asymmetry in schizophrenia Meta-analysis. BJP. 2001 4;178(4):344–51.

36. Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP. A forkhead-domain gene is mutated in a severe speech and language disorder. Nature. 2001 4;413(6855):519–23.

37. Spiteri E, Konopka G, Coppola G, Bomar J, Oldham M, Ou J, et al. Identification of the transcriptional targets of FOXP2, a gene linked to speech and language, in developing human brain. Am. J. Hum. Genet. 2007;81(6):1144–57.

38. Sanjuan J, Tolosa A, González JC, Aguilar EJ, Moltó MD, Nájera C, et al. FOXP2 polymorphisms in patients with schizophrenia. Schizophrenia Research. 2005 1;73(2–3):253–6.

39. Sanjuán J, Tolosa A, González JC, Aguilar EJ, Pérez-Tur J, Nájera C, et al. Association between FOXP2 polymorphisms and schizophrenia with auditory hallucinations. Psychiatr. Genet. 2006;16(2):67–72.

40. Fisher SE, Scharff C. FOXP2 as a molecular window into speech and language. Trends in Genetics. 2009;25(4):166–77.

41. Andreasen NC, Flaum M. Schizophrenia: The Characteristic Symptoms. Schizophrenia Bulletin. 1991 1;17(1):27 –49.

42. Cummings JL, Miller BL. Visual Hallucinations: Clinical Occurrence and Use in Differential Diagnosis. Western Journal of Medicine. 1987;146(1):46.

43. Bracha HS, Wolkowitz OM, Lohr JB, Karson CN, Bigelow LB. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. Am J Psychiatry. 1989;146(4):526–8.

44. Behrendt R-P. Contribution of hippocampal region CA3 to consciousness and schizophrenic hallucinations. Neuroscience & Biobehavioral Reviews. 2010;34(8):1121–36.

45. Friston KJ. The disconnection hypothesis. Schizophrenia Research. 1998 10;30(2):115–25.

46. Stephan KE, Baldeweg T, Friston KJ. Synaptic Plasticity and Dysconnection in Schizophrenia. Biological Psychiatry. 2006 15;59(10):929–39.

47. Stephan KE, Friston KJ, Frith CD. Dysconnection in Schizophrenia: From Abnormal Synaptic Plasticity to Failures of Self-monitoring. Schizophrenia Bulletin. 2009 1;35(3):509 –527.

48. Le Strat Y, Ramoz N, Gorwood P. The role of genes involved in neuroplasticity and neurogenesis in the observation of a gene-environment interaction (GxE) in schizophrenia. Curr. Mol. Med. 2009;9(4):506–18.

49. Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, et al. Modelling schizophrenia using human induced pluripotent stem cells. Nature. 2011 12;473(7346):221–5.

50. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch. Gen. Psychiatry. 2003;60(12):1187–92.

51. Zhang LI, Poo MM. Electrical activity and development of neural circuits. Nat. Neurosci. 2001;4 Suppl:1207–14.

52. Hua JY, Smith SJ. Neural activity and the dynamics of central nervous system development. Nat. Neurosci. 2004;7(4):327–32.

53. Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. Neuron. 2012 21;74(6):990–1004.

54. Allen P, Modinos G, Hubl D, Shields G, Cachia A, Jardri R, et al. Neuroimaging Auditory Hallucinations in Schizophrenia: From Neuroanatomy to Neurochemistry and Beyond. Schizophrenia bulletin. 2012 25;

55. Rotarska-Jagiela A, Oertel-Knoechel V, DeMartino F, van de Ven V, Formisano E, Roebroeck A, et al. Anatomical brain connectivity and positive symptoms of schizophrenia: A diffusion tensor imaging study. Psychiatry Research: Neuroimaging. 2009 30;174(1):9–16.

56. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes. Mol Psychiatry. 2009 19;14(8):746–54.

ARTICLE 3

The hippocampal complex at the cross-road of dimensional/categorical approaches

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THE HIPPOCAMPAL COMPLEX AT THE CROSS-ROAD OF DIMENSIONAL/CATEGORICAL APPROACHES

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LETTER IN REPLY (Correspondence)
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Rasetti and colleagues[1] recently wrote a stimulating paper that highlighted the major role played by the hippocampal complex (HC; i.e., the hippocampus and para-hippocampal gyri) in the pathophysiology of schizophrenia (SCZ). These authors claimed that SCZ patients and their healthy siblings exhibited reduced bilateral parahippocampal activity and hippocampal-parietal (BA 40) coupling during the encoding of novel stimuli when compared with matched healthy controls. The authors indicated that these findings may support the potential role of the hippocampal-parahippocampal function during encoding as an intermediate biological phenotype related to an increased genetic risk for SCZ.

Because SCZ is heterogeneous, we would like to complementarily defend the idea that subtle clinical and phenomenological explorations may help further our understanding of the specific pathophysiological processes related to the HC that would require integration in a dimensional framework.

Impairments in the HC have been repeatedly reported in SCZ, e.g., including reductions in volume, increases in basal perfusion, activation deficits during declarative memory and reductions in neurogenesis in the dentate gyrus[2]. In Rasetti et al., the reference to a 3-group design that incorporates individuals at a high genetic-risk for SCZ effectively allows the disentanglement of trait vs. state features[3] of the HC in the SCZ spectrum. Recent data have also highlighted the crucial distinction that must be made between disease-specific and symptom-specific effects on HC connectivity. While examining carefully selected SCZ patients with auditory-only or audio-visual hallucinations who were otherwise matched for PANSS scores and antipsychotic dosages, Amad and colleagues recently showed differential HC connectivity patterns depending on the sensory-modality involved in hallucinatory experiences[4]. By focusing on the presence or absence of visual hallucinations in SCZ patients who suffer from auditory hallucinations, these authors showed that the HC was specifically involved in audiovisual hallucinations independently of the SCZ factor.

The dimensional approach proposed by Amad et al. allowed for the reduction of the impact of clinical heterogeneity on imaging findings and explored HC multimodal connectivity within and across domains. Such an approach was recently encouraged by the NIMH through the RDoC initiative[5]. Because it also works for common basic clinical/biological features between various disorders, the dimensional approach paves the way for transnosographical explorations of intermediate phenotypes (i.e., in SCZ sub-populations, in individuals at genetic risks or in healthy individuals experiencing sub-clinical symptoms, e.g., in healthy individuals who hear voices) and thus aids in realizing the goal of defining new imaging-based biomarkers in psychiatry.

1. Rasetti R, Mattay VS, White MG, et al. Altered hippocampal-parahippocampal function during stimulus encoding: A potential indicator of genetic liability for schizophrenia. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2013.3911.
2. Tamminga CA, Stan AD, Wagner AD. The Hippocampal Formation in Schizophrenia. *Am J Psychiatry*. 2010;167(10):1178–1193. doi:10.1176/appi.ajp.2010.09081187.
3. Gottesman II, Gould TD. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am J Psychiatry*. 2003;160(4):636–645. doi:10.1176/appi.ajp.160.4.636.
4. Amad A, Cachia A, Gorwood P, et al. The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations. *Mol Psychiatry*. 2014. doi:10.1038/mp.2012.181

5. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *Am J Psychiatry*. 2010;167(7):748–751. doi:10.1176/appi.ajp.2010.09091379.

ARTICLE 4

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

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THE MULTIMODAL CONNECTIVITY OF THE HIPPOCAMPAL COMPLEX IN AUDITORY AND VISUAL HALLUCINATIONS

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Abstract

Hallucinations constitute one of the most representative and disabling symptoms of schizophrenia. Several 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, i.e., 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.

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

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; i.e., 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[13,14] and environmental factors[15], leading to early alterations in the development of brain wiring and impaired experience-dependent synaptic plasticity[11].

A proof of concept for dysconnectivity in schizophrenic patients suffering from auditory hallucinations has recently been provided. Functional connectivity (FC), which is based on the 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 auditory hallucinations in comparison with non-hallucinating patients or healthy controls[16,17]. No specific FC study has been conducted for non-auditory hallucinations; 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 auditory hallucinations but also during visual and multisensory hallucinations[18].

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 areas in patients with auditory hallucinations in comparison with non-hallucinating patients

or healthy controls[19–24]. An interpretation of variations in FA is not straightforward; however, a reduced FA is commonly interpreted as a loss in white matter integrity[17,25], whereas an increased FA is thought to reflect an increase in white matter connectivity[26]. 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[27]. 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[28]. 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[28]). In addition, hippocampal hyperactivity has been regularly associated with hallucinations in patients with schizophrenia[6, 29–31]. As noted by R-P Behrendt, the presence of visual hallucinations, in combination with auditory hallucinations, indicates pathologically increased hippocampal activity[32]. In agreement with this hypothesis, Oertel and colleagues 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[33]. Finally, electrical stimulation of the HC can produce complex visual hallucinations in epileptic patients[34].

In this paper, we explored HC connectivity in two subgroups of carefully selected patients with schizophrenia: those with only auditory hallucinations (AH) (i.e., patients that 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. Moreover, this design allows for the assessment of the specific effects of the hallucinatory modality, which are to be distinguished from effects that are more related to schizophrenia and medication. Such a distinction appears crucial in testing the hypothesis that variable patterns of brain connectivity in hallucinators according to the sensory modality involved, which goes further than the conventional comparison between patients with schizophrenia and healthy controls.

Joint multimodal data analysis of HC connectivity, including FC, structural white matter integrity and shape analysis, was used to separately unravel the relationships partially detected by structural and functional measures alone[35]. 1) Functional resting-state connectivity was performed in

A+VH and AH patients. This analysis was seeded on the bilateral HC. Specific connected network function of sensory modalities involved were anticipated. 2) FA maps were then compared between A+VH and AH patients. A specific implication of the HC in visual hallucinations was anticipated, which could result in a higher structural connectivity between HC and visual areas in A+VH patients. 3) deformability of the hippocampus, a structure capable of experience-dependent plasticity[36], was considered as a potential indirect marker of these patterns of connectivity. Shape analysis compared both groups. Based on our hypothesis, 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 based on interviews and review of their clinical history by an experienced psychiatrist. The Positive and Negative Syndrome Scale (PANSS)[37] and the Scale for the Assessment of Positive Symptoms (SAPS)[38] were used to evaluate 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 auditory hallucinations (SAPS-it. #1 ≥ 4). Patients from the AH group had never experienced visual hallucinations (i.e., SAPS-it. #6 = 0), whereas A+VH patients scored greater than 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 based on medical history and medical and neurological examination. None of the patients reported substance abuse with the exception of 4 patients with the occasional consumption of cannabis (2 in AH group and 2 in A+VH group). No patient with an IQ below 80 was included. Groups were matched for age, sex, handedness, symptom severity, auditory hallucinations, 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[39]. 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.

INSERT TABLE 1 ABOUT HERE

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 (FDT), which is part of FMRIB Software Library (FSL)[40] (FSL 4.1.9, Oxford, www.fmrib.ox.ac.uk/fsl). The detailed MR sequence parameters and pre-processing 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 (GLM) 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 GLM: white matter signal, cerebro-spinal fluid signal, and head-motion parameters (x/y/z corrections applied in translation and rotation).

After fitting the GLM and accounting for the effects of temporal serial correlation using AR(2) modeling, a random effects GLM 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[41].

Tract-based spatial statistics. Tract-Based Spatial Statistics (TBSS)[42], a part of FSL, was used for the voxel-wise statistical analysis of FA map using standard parameters to study white matter integrity. FA maps were first aligned into a common space using the nonlinear registration tool *FNIRT*, which uses a b-spline representation of the registration warp field[43]. 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 (randomized function, implemented in FSL). Contrasts between the AH and A+VH groups were based on 10,000 randomized permutations with age introduced as a covariate.

Statistic threshold strategy. Cluster-size thresholding via Monte Carlo simulations[44] was applied to the sb-FC results to correct the statistical maps for multiple comparisons[45]. A P-value < 0.05 was considered significant. For TBSS, the significance of integrating corrections for multiple pairwise comparisons (*False Discovery Rate*, i.e., 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, and volumes were corrected for whole-brain volume using the SIENAX, part of FSL. Between-group volumetric differences were calculated using analyses of covariance (ANCOVA) with the whole-brain volume as a covariate. For the shape analysis, a surface mesh was created using a Bayesian modeling framework[46]. 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[47]. 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**.

INSERT TABLE 1 ABOUT HERE

Hippocampal complex functional connectivity

Group-level RFX-ANCOVA of HC sb-FC revealed increased connectivity in A+VH patients when compared to the AH group between HC and the *bilateral medial prefrontal cortex* (mPFC) and the *left caudate nucleus* (CN) 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 ($\mathbf{P_{corr} < 0.05}$) are reported in **Table 2**.

INSERT FIGURE 1 AND TABLE 2 ABOUT HERE

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 to 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); $\mathbf{P_{corr} < 0.03}$), the *right inferior fronto-occipital fasciculus* ((36,-56,6), $\mathbf{P_{corr} < 0.04}$), the *left inferior longitudinal fasciculus* ((-49,-24,-18); $\mathbf{P_{corr} < 0.04}$), the *left cingulum* ((10,42,31); $\mathbf{P_{corr} < 0.03}$), the *left superior longitudinal fasciculus* ((-27,33,53); $\mathbf{P_{corr} < 0.02}$), and the *brainstem* ((-2,-26,-26); $\mathbf{P_{corr} < 0.03}$).

INSERT FIGURE 2 ABOUT HERE

Hippocampal volume and shape analysis

Absolute hippocampal volumes were significantly increased in the A+VH group (left/right hippocampal volumes: 2 302.7 mm^3 ± 1 347.3 / 2 338.3 mm^3 ± 1 341.9 mm^3) compared to the AH group (left/right hippocampal volumes: 3 683.7 mm^3 ± 1 356.3 / 3 665.2 mm^3 ± 1 203.5 mm^3) (**P < 0.01**). This result remained significant after correcting for whole-brain volume (**P < 0.01**). The difference between the left and right hippocampus was not significant (P = 0.9).

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 to the AH group.

INSERT FIGURE 3 ABOUT HERE

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, increased functional connectivity of the HC with the mPFC 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 mPFC and the ventral striatum[48]. These structures send projections to the ventral tegmental area (VTA), a dopamine projection-system that projects to the cortex[48]. Previous research has not shown whether the increased tone in dopaminergic striatal pathways observed in schizophrenia correlates with the severity of positive symptoms and, thus, whether this increased tone is a state (i.e., presence/absence of the symptoms) or a trait (linked to the schizophrenia vulnerability) feature of the disorder[49,50]. The current findings are consistent with the idea that increased dopaminergic transmission may lead to more complex hallucinatory experiences in schizophrenia (i.e., one supplementary sensory modality in A+VH patients). Patients with auditory-only hallucinations also exhibited a higher sb-FC between the HC and the thalamus in comparison with the A+VH group.

Interestingly, some authors have already suggested that auditory hallucinations 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[32,51]. 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[52] through the lentiform nucleus[53], were strongly functionally connected with the HC in AH patients. Of note, all of these regions, which are crucial for language processing[54], were previously shown to be activated, together with the pre- and post-central gyri, during auditory hallucinations in both psychotic and nonpsychotic subjects[55]. In addition, we confirmed that the particular functional connectivity patterns measured here were specific to the sensory modality involved in hallucinatory experiences, (i.e., AH or A+VH) rather than the underlying disorder (i.e., 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 based on 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[56,57]. 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[58]), 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[59]). 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 sub-fields. 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", i.e., the feed-forward connectivity with the striatum and the prefrontal cortex and the feedback connectivity with visual areas[60] (connections that were both noted to be increased in A+VH patients). Indeed, the hippocampus is capable of plastic deformation[61], and the present findings are consistent with experience-dependent shape modifications of the hippocampus that involve mechanical tension along the axon[62]. 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[63]. 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[63]. Moreover, a negative correlation has recently been shown between the PANSS-positive sub-scale 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[64]. 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[65] in such a context, and this adequacy appears to be reinforced by the use of a multimodal design that provides convergent findings. 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 play a central role in basic information processing and positive symptoms[66]. 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 grey matter reductions within the language network of patients with auditory hallucinations to be plastic adaptations related to the hallucinations themselves[67,68] and extends them to other sensory modalities. Based on 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[69]. 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[70].

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 (rTMS), a noninvasive and painless technique currently used for this indication[71], induces neuroplastic changes and modifications of the FC of the temporo-parietal junction, a target chosen for its involvement in auditory hallucinations[72,73]. Current findings fully support the future development of therapeutic strategies to address extra-auditory hallucinations based on neuro-guided rTMS, which could modulate the connection strength of specific neural networks, such as the networks identified in the present study (e.g., 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 schizophrenic patients suffering from auditory hallucinations, 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.

Acknowledgments

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TABLES AND FIGURES CAPTIONS

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

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. Correction for multiple comparisons was performed using Monte Carlo simulations at the cluster level.

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; $\mathbf{P_{corr} < 0.05}$). 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 (LN), the right thalamus and the superior temporal gyri (STG) (**lower panel**).

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; $\mathbf{P_{corr} < 0.05}$). 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.

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.

REFERENCES

1. Andreasen NC, Flaum M. Schizophrenia: The Characteristic Symptoms. *Schizophrenia Bulletin* 1991; **17**: 27 –49.

2. Cummings JL, Miller BL. Visual Hallucinations: Clinical Occurrence and Use in Differential Diagnosis. *Western Journal of Medicine* 1987; **146**: 46.

3. Bracha HS, Wolkowitz OM, Lohr JB, Karson CN, Bigelow LB. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. *Am J Psychiatry* 1989; **146**: 526–8.

4. Braun CMJ, Dumont M, Duval J, Hamel-Hébert I, Godbout L. Brain modules of hallucination: an analysis of multiple patients with brain lesions. *Journal of Psychiatry and Neuroscience* 2003; **28**: 432.

5. Allen P, Larøi F, McGuire PK, Aleman A. The hallucinating brain: A review of structural and functional neuroimaging studies of hallucinations. *Neuroscience & Biobehavioral Reviews* 2008; **32**: 175–91.

6. Jardri R, Pouchet A, Pins D, Thomas P. Cortical Activations During Auditory Verbal Hallucinations in Schizophrenia: A Coordinate-Based Meta-Analysis. *Am J Psychiatry* 2011; **168**: 73–81.

7. Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, Trouard T, *et al.* Hippocampal complex and retrieval of recent and very remote autobiographical memories: Evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus* 2001; **11**: 707–14.

8. Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. *Neuron* 2012; **74**: 990–1004.

9. ffytche DH. The hodology of hallucinations. *Cortex* 2008; **44**: 1067–83.

10. Friston KJ. The disconnection hypothesis. *Schizophrenia Research* 1998; **30**: 115–25.

11. Stephan KE, Baldeweg T, Friston KJ. Synaptic Plasticity and Dysconnection in Schizophrenia. *Biological Psychiatry* 2006; **59**: 929–39.

12. Stephan KE, Friston KJ, Frith CD. Dysconnection in Schizophrenia: From Abnormal Synaptic Plasticity to Failures of Self-monitoring. *Schizophrenia Bulletin* 2009; **35**: 509 –527.

13. Le Strat Y, Ramoz N, Gorwood P. The role of genes involved in neuroplasticity and neurogenesis in the observation of a gene-environment interaction (GxE) in schizophrenia. *Curr Mol Med* 2009; **9**: 506–18.

14. Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, *et al.* Modelling schizophrenia using human induced pluripotent stem cells. *Nature* 2011; **473**: 221–5.

15. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 2003; **60**: 1187–92.

16. Hoffman RE, Hampson M. Functional connectivity studies of patients with auditory verbal hallucinations. *Front Hum Neurosci* 2012; **6**: 6.

17. Allen P, Modinos G, Hubl D, Shields G, Cachia A, Jardri R, *et al.* Neuroimaging Auditory Hallucinations in Schizophrenia: From Neuroanatomy to Neurochemistry and Beyond. *Schizophrenia bulletin* 2012;

18. Jardri R, Thomas P, Delmaire C, Delion P, Pins D. The Neurodynamic Organization of Modality-Dependent Hallucinations. *Cereb Cortex* 2012;

19. Hubl D, Koenig T, Strik W, Federspiel A, Kreis R, Boesch C, *et al.* Pathways That Make Voices: White Matter Changes in Auditory Hallucinations. *Arch Gen Psychiatry* 2004; **61**: 658–68.

20. Shergill SS, Kanaan RA, Chitnis XA, O'Daly O, Jones DK, Frangou S, *et al.* A Diffusion Tensor Imaging Study of Fasciculi in Schizophrenia. *Am J Psychiatry* 2007; **164**: 467–73.

21. Rotarska-Jagiela A, Oertel-Knoechel V, DeMartino F, van de Ven V, Formisano E, Roebroeck A, *et al.* Anatomical brain connectivity and positive symptoms of schizophrenia: A diffusion tensor imaging study. *Psychiatry Research: Neuroimaging* 2009; **174**: 9–16.

22. de Weijer AD, Neggers SFW, Diederen KMS, Mandl RCW, Kahn RS, Pol H, *et al.* Aberrations in the arcuate fasciculus are associated with auditory verbal hallucinations in psychotic and in non-psychotic individuals. *Human Brain Mapping* 2011;

23. Catani M, Craig MC, Forkel SJ, Kanaan R, Picchioni M, Toulopoulou T, *et al.* Altered Integrity of Perisylvian Language Pathways in Schizophrenia: Relationship to Auditory Hallucinations. *Biological Psychiatry* 2011; **70**: 1143–50.

24. de Weijer AD, Mandl RCW, Diederen KMJ, Neggers SFW, Kahn RS, Pol HEH, *et al.* Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. *Schizophrenia Research* 2011; **130**: 68–77.

25. Johansen-Berg H, Rushworth MFS. Using diffusion imaging to study human connectional anatomy. *Annu Rev Neurosci* 2009; **32**: 75–94.

26. Dong Q, Welsh RC, Chenevert TL, Carlos RC, Maly-Sundgren P, Gomez-Hassan DM, *et al.* Clinical applications of diffusion tensor imaging. *Journal of Magnetic Resonance Imaging* 2004; **19**: 6–18.

27. Ashtari M, Cottone J, Ardekani BA, Cervellione K, Szeszko PR, Wu J, *et al.* Disruption of white matter integrity in the inferior longitudinal fasciculus in adolescents with schizophrenia as revealed by fiber tractography. *Arch Gen Psychiatry* 2007; **64**: 1270–80.

28. Tamminga CA, Stan AD, Wagner AD. The Hippocampal Formation in Schizophrenia. *Am J Psychiatry* 2010; **167**: 1178–93.

29. Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RS. Patterns of cerebral blood flow in schizophrenia. *The British Journal of Psychiatry* 1992; **160**: 179 –186.

30. Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootoonk S, *et al.* A functional neuroanatomy of hallucinations in schizophrenia. *Nature* 1995; **378**: 176–9.

31. Liddle PF, Lane CJ, Ngan ETC. Immediate effects of risperidone on cortico—striato—thalamic loops and the hippocampus. *The British Journal of Psychiatry* 2000; **177**: 402 –407.

32. Behrendt R-P. Contribution of hippocampal region CA3 to consciousness and schizophrenic hallucinations. *Neuroscience & Biobehavioral Reviews* 2010; **34**: 1121–36.

33. Oertel V, Rotarska-Jagiela A, van de Ven VG, Haenschel C, Maurer K, Linden DEJ. Visual hallucinations in schizophrenia investigated with functional magnetic resonance imaging. *Psychiatry Research: Neuroimaging* 2007; **156**: 269–73.

34. Vignal J-P, Maillard L, McGonigal A, Chauvel P. The dreamy state: hallucinations of autobiographic memory evoked by temporal lobe stimulations and seizures. *Brain* 2007; **130**: 88 –99.

35. Sui J, Yu Q, He H, Pearlson GD, Calhoun VD. A selective review of multimodal fusion methods in schizophrenia. *Front Hum Neurosci* 2012; **6**: 27.

36. Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, *et al.* Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci USA* 2000; **97**: 4398–403.

37. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin* 1987; **13**: 261 –276.

38. Andreasen NC. Methods for assessing positive and negative symptoms. *Mod Probl Pharmacopsychiatry* 1990; **24**: 73–88.

39. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International Consensus Study of Antipsychotic Dosing. *American Journal of Psychiatry* 2010; **167**: 686–93.

40. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, *et al.* Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 2004; **23, Supplement 1**: S208–S219.

41. David CN, Greenstein D, Clasen L, Gochman P, Miller R, Tossell JW, *et al.* Childhood Onset Schizophrenia: High Rate of Visual Hallucinations. *Journal of the American Academy of Child & Adolescent Psychiatry* 2011; **50**: 681–686.e3.

42. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, *et al.* Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage* 2006; **31**: 1487–505.

43. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* 1999; **18**: 712–21.

44. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 1995; **33**: 636–47.

45. Goebel R, Esposito F, Formisano E. Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: From single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Human Brain Mapping* 2006; **27**: 392–401.

46. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *NeuroImage* 2011; **56**: 907–22.

47. Frisoni GB, Sabattoli F, Lee AD, Dutton RA, Toga AW, Thompson PM. In vivo neuropathology of the hippocampal formation in AD: A radial mapping MR-based study. *NeuroImage* 2006; **32**: 104–10.

48. Thierry A-M, Gioanni Y, Dégénétais E, Glowinski J. Hippocampo-prefrontal cortex pathway: Anatomical and electrophysiological characteristics. *Hippocampus* 2000; **10**: 411–9.

49. Howes OD, Montgomery AJ, Asselin M, Murray RM, Grasby PM, McGUIRE PK. Molecular Imaging Studies of the Striatal Dopaminergic System in Psychosis and Predictions for the Prodromal Phase of Psychosis. *BJP* 2007; **191**: s13–s18.

50. Valli I, Howes O, Tyrer P, McGuire P, Grasby PM. Longitudinal PET Imaging in a Patient With Schizophrenia Did Not Show Marked Changes in Dopaminergic Function With Relapse of Psychosis. *American Journal of Psychiatry* 2008; **165**: 1613–4.

51. Behrendt R-P, Young C. Hallucinations in schizophrenia, sensory impairment, and brain disease: a unifying model. *Behav Brain Sci* 2004; **27**: 771–787; discussion 787–830.

52. Shim YS, Kim J-S, Shon YM, Chung Y-A, Ahn K-J, Yang D-W. A serial study of regional cerebral blood flow deficits in patients with left anterior thalamic infarction: Anatomical and neuropsychological correlates. *Journal of the Neurological Sciences* 2008; **266**: 84–91.

53. Byrne JH (ed. ., Gray L. *Neuroscience Online: An Electronic Textbook for the Neurosciences http://nba.uth.tmc.edu/neuroscience/*. Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston (UTHealth)© 1997-2012, all rights reserved:

54. Ojemann GA. Cortical Organization of Language. *J Neurosci* 1991; **11**: 2281–7.

55. Diederen KMJ, Daalman K, Weijer D, D A, Neggers SFW, Van Gastel W, *et al.* Auditory Hallucinations Elicit Similar Brain Activation in Psychotic and Nonpsychotic Individuals. *Schizophr Bull* 2011;

56. Gloor P, Salanova V, Olivier A, Quesney LF. The human dorsal hippocampal commissure. An anatomically identifiable and functional pathway. *Brain* 1993; **116**: 1249–73.

57. Burgess PW, Veitch E, de Lacy Costello A, Shallice T. The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia* 2000; **38**: 848–63.

58. Catani M, Jones DK, Donato R, Ffytche DH. Occipito-Temporal Connections in the Human Brain. *Brain* 2003; **126**: 2093–107.

59. Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS, *et al.* Segmentation of Subcomponents Within the Superior Longitudinal Fascicle in Humans: A Quantitative, In Vivo, DT-MRI Study. *Cereb Cortex* 2005; **15**: 854–69.

60. Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews Neuroscience* 2011; **12**: 585–601.

61. Leutgeb JK, Leutgeb S, Treves A, Meyer R, Barnes CA, McNaughton BL, *et al.* Progressive Transformation of Hippocampal Neuronal Representations in 'Morphed' Environments. *Neuron* 2005; **48**: 345–58.

62. Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 1997; **385**: 313–8.

63. Qiu A, Tuan TA, Woon PS, Abdul-Rahman MF, Graham S, Sim K. Hippocampal-cortical structural connectivity disruptions in schizophrenia: An integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles. *NeuroImage* 2010; **52**: 1181–9.

64. Kühn S, Musso F, Mobascher A, Warbrick T, Winterer G, Gallinat J. Hippocampal subfields predict positive symptoms in schizophrenia: First evidence from brain morphometry. *Translational Psychiatry* 2012; **2**: e127.

65. Carter CS, Heckers S, Nichols T, Pine DS, Strother S. Optimizing the Design and Analysis of Clinical Functional Magnetic Resonance Imaging Research Studies. *Biological Psychiatry* 2008; **64**: 842–9.

66. Meyer-Lindenberg A. From maps to mechanisms through neuroimaging of schizophrenia. *Nature* 2010; **468**: 194–202.

67. Hubl D, Dougoud-Chauvin V, Zeller M, Federspiel A, Boesch C, Strik W, *et al.* Structural analysis of Heschl's gyrus in schizophrenia patients with auditory hallucinations. *Neuropsychobiology* 2010; **61**: 1–9.

68. van Swam C, Federspiel A, Hubl D, Wiest R, Boesch C, Vermathen P, *et al.* Possible dysregulation of cortical plasticity in auditory verbal hallucinations–A cortical thickness study in schizophrenia. *Journal of Psychiatric Research*

69. Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, *et al.* Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends in Neurosciences* 2008; **31**: 234–42.

70. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes. *Mol Psychiatry* 2009; **14**: 746–54.

71. 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; **71**: e15–16.

72. Hoffman RE, Hampson M, Wu K, Anderson AW, Gore JC, Buchanan RJ, *et al.* Probing the Pathophysiology of Auditory/Verbal Hallucinations by Combining Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation. *Cerebral Cortex* 2007; **17**: 2733 – 2743.

73. Vercammen A, Knegtering H, Liemburg EJ, Boer JA den, Aleman A. Functional connectivity of the temporo-parietal region in schizophrenia: Effects of rTMS treatment of auditory hallucinations. *Journal of Psychiatric Research* 2010; **44**: 725–31.

ARTICLE 5

Resting-State Functional Connectivity of the Nucleus Accumbens in Auditory and Visual Hallucinations in Schizophrenia

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ARTICLE 6

Deviations in cortex sulcation associated with visual hallucinations in schizophrenia

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Article soumis, en révision

DEVIATIONS IN CORTEX SULCATION ASSOCIATED WITH VISUAL HALLUCINATIONS IN SCHIZOPHRENIA

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Running title: Cortex sulcation and visual hallucinations

Authors 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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Abstract

Hallucinations, and auditory hallucinations (AH) in particular, constitute the most typical and disabling symptoms of schizophrenia. Although visual hallucinations (VH) have been largely neglected in psychiatric disorders, a recent review reported a 27% mean prevalence of VH in schizophrenic patients. The pathophysiology underlying VH in schizophrenia remains elusive. Because several schizophrenia studies reported a significant effect of age on VH, 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 and in two subgroups of carefully selected schizophrenia patients suffering from hallucinations: patients with only AH (i.e., patients who never reported VH) and patients with audio-visual hallucinations (A+VH). As expected, different hemispheric cortical sulcation, i.e., the ratio between total sulcal area and outer cortex area, was measured in A+VH and AH patients. Although a specific association between VH and neurodegenerative mechanisms, e.g., 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.

Keywords: schizophrenia, sulcation, neurodevelopment, visual hallucinations, MRI

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 of 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 (i.e., 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 visual and auditory hallucinations co-occur in up to 84% of individuals with schizophrenia[7], while for other authors, VH were considered to never occur in isolation in schizophrenia patients[8].

The pathophysiology and pathogenesis of underlying hallucinations in schizophrenia remain elusive and complex. Indeed, in comparison with neurological disorders, hallucinations observed in schizophrenia are not related to focal neurologic 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 in childhood-onset schizophrenia also suggested that VH could be considered a severity index of neurodevelopmental abnormalities[18].

In this context, the present study was aimed at testing the hypothesis of neurodevelopmental deviations associated with VH in schizophrenia. We compared healthy controls (HC) to two subgroups of carefully selected schizophrenia patients with hallucinations: patients with

only AH (i.e., 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. Moreover, the 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 (indeed, specific effects of VH must be distinguished from disease- or medication-related effects).

MATERIAL AND METHODS

Participants

Thirty-three outpatients suffering from schizophrenia[10] and 16 healthy controls (HC) were included in the study. 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)[19] and the Scale for the Assessment of Positive Symptoms (SAPS)[20] were used to evaluate general psychopathology and to quantify symptomatology. All patients received these semi-structured interviews, which included a detailed assessment of their lifetime hallucinatory experiences. All patients were noted to have marked-to-severe auditory hallucinations (SAPS-it. #1 ≥ 4). Patients from the AH group had never experienced visual hallucinations (i.e., SAPS-it. #6 = 0), whereas A+VH patients scored greater than 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 based on medical history and medical and neurological examination. None of the patients reported substance abuse, with the exception of 4 patients reporting the occasional consumption of cannabis (2 in AH group and 2 in A+VH group). No patient with an IQ 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, 21]. 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[22]. 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**.

INSERT TABLE 1 ABOUT HERE

MRI acquisition

All patients underwent a 10-minute anatomical T1-weighted sequence (3D 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, The Netherlands). All patients wore headphones and earplugs to attenuate the noise of the scanner. These MRIs were adapted to the reconstruction of the fine individual cortical folds[13].

Measure of cortex sulcation

To assess both global and regional cortex morphology, 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 to the investigation of cortical folding abnormalities in patients with schizophrenia[13, 23, 24] and bipolar disorder[25, 26]. 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], grey 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 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[27]. 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 due to the sulcus shape deformations induced by the warping process.

INSERT FIGURE 1 ABOUT HERE

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 (i.e., the sum of the areas of all segmented cortical folds) and the total outer cortex area (**Figure 1 A-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 1 D). At 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 (GI), the ratio of the whole gyral contour length to the outer, exposed surface[28], which embodies additional information (included in the whole gyral contour length) related to the cortex thickness and the sulcal opening. In addition, the classical GI captures the shape of the cortical folds, which are complex three-dimensional structures from measures on two-dimensional MRI slices[28], while 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[29] (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, pre-central 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 (i.e., “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 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. In addition, explorative regional post hoc comparisons between AH and A+VH were performed on the twelve predefined hemispheric regional sulcal indexes (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 linear models. A two-tailed p value of less than 0.05 was considered statistically significant. All the statistical analyses were carried out with R 2.12 software (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 between HC, patients with A+VH and patients with AH (i.e., significant main effect of the group, $F = 108$; d.f.=2; $p < 0.0005$), and this effect varied with hemisphere as witnessed 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 difference between AH and A+VH patients on right hemisphere ($T=2.26$, d.f.=31; $p = 0.03$) with a g-SI decrease in patients with A+VH (1.55±0.03) compared to 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 to patients with AH (1.59±0.03) was not significant ($T=1.55$; d.f.=31; $p=0.12$). Of note, addition of normalized hemispheric GM or WM volumes, outer cortex area or cumulative treatment dose as covariate in g-SI analyses yielded similar results. The between-group differences in hemispheric g-SI were not accounted for by differences in outer cortex surface area. Indeed, in the left hemisphere, the outer cortical area was 431.52±8.36 cm^2 in 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 cm^2 and 431.72±8.79 cm^2 ($T=0.12$; d.f.=31; $p=0.90$).

Post hoc analyses also revealed highly significant bilateral differences between HC and schizophrenia subgroups with a greater g-SI in HC in the left (2.07±0.03) and right (2.11±0.03) hemispheres compared to patients with AH ($T>10.9$, d.f.=31, $p < 0.0005$) or A+VH ($T>12.9$, d.f.=31, $p < 0.0005$).

INSERT FIGURE 2 ABOUT HERE

These findings were specific for the cortex sulcation as mixed-design repeated measures ANOVA revealed no main or interactive effects of group, 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**.

INSERT TABLE 2 ABOUT HERE

Explorative regional analyses

Regional post hoc analyses in patient revealed that the sulcation decrease in patients with A+VH was not uniform: there was a decreased regional sulcation index (r-SI) in the right superior parietal cortex (**F=4.92**; d.f.=1; **p=0.03**) in A+VH patients (0.192±0.006) compared with AH patients (0.213±0.006) as well as in the left sylvian fissure (**F=4.57**; d.f.=1; **p=0.04**) in A+VH patients (0.040±0.004) compared with AH patients (0.054±0.004). These regional findings should be considered as exploratory because none held following Bonferroni correction for multiple testing (α-corrected=0.002, i.e., 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. As expected, different cortical sulcation was found between A+VH and AH patients, with decreased sulcation in A+VH patients.

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[30]. Hence, our findings provide evidence of a neurodevelopmental origin for VH in schizophrenia, in line with clinical studies showing that VH are associated with early disturbances in brain development[16-18].

Several factors contribute to the neurodevelopmental processes that influence the shape of the folded cerebral cortex[12], including structural connectivity through axonal tension forces[31, 32]. These mechanical constraints lead to a compact layout that optimizes the transmission of neuronal signals between brain regions[33] and thus brain network functioning. Furthermore, experimental lesion studies in monkeys indicate that the disruption of afferent pathways, when occurring early in pregnancy, before the formation of cortical pathways linking the visual areas, can lead to the emergence of abnormal sulcation in the occipital lobe[34, 35]. A similar early difference in white matter 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, 36].

Considering VH as a marker of deviations during 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 (NSS) – i.e., observable defects in motor coordination, motor integration and sensory integration[37] related to pre- and peri-natal impairments[38-40] - have also been found associated with decreased sulcation[24].

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 [41-44] and more recently during audio-visual hallucinations[45]. 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 anti-correlated during the experience of hallucinations. Furthermore the DMN spatial and temporal instability persisted during non-hallucinatory periods[45]. Interestingly, impaired interactions with the DMN have also been suggested in the pathophysiology of VH in Parkinson Disease (PD)[46], 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[46].

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 a difference in the fractional anisotropy, a diffusion MRI marker of local white matter 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[47], and their shape is difficult to reliably describe based on two-dimensional MRI slices[27]. The use of 3D mesh-based sulcal indexes[13] has provided an accurate assessment of the cortex morphology as in our previous studies in schizophrenia[13, 15, 23, 24]. This study focused on sulcation because cortical sulci can be reliably defined using simple geometric properties[27], while the gyri are relatively difficult to reliably define from a purely geometrical point of view, especially for the borders not limited by sulci[48]. 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 provided evidence for specific association between VH and neurodegenerative mechanisms (e.g., 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[49] in VH patients, coupled with pathway analyses[50] of genes involved in neurodevelopment and neuroplasticity.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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TABLES AND FIGURES CAPTIONS

Table 1. Demographical and clinical characteristics of the 33 patients with schizophrenia based on the presence of auditory only or audio-visual hallucinations. Quantitative (resp. qualitative) demographic and clinical characteristics comparisons between AH and A+VH patients were based on bilateral Student's t (resp. Chi-2) tests.

Table 2. Results of global sulcal index (g-SI) and global volumes analyses. Data are presented as means (standard error of the mean). Variables significantly different between patients with auditory hallucinations (AH) and patients with audio-visual hallucinations (A+VH) are indicated by bold font (patients with auditory hallucinations (AH) as reference). All results were linearly adjusted for age and gender. [*GM: Grey Matter; WM: White Matter; CSF: Cerebro-Spinal Fluid*]

Figure 1. **Three-dimensional segmentation of the cortical folds and global sulcal index (g-SI).** Automatically segmented cortical folds (A, C; in red) and smooth envelope of the brain mask (A, B; in blue) represented on 2D MRI slices (A: coronal) and using mesh-based 3D reconstruction (B: brain hull surface - C: cortical sulci and brain surface). D: Reconstructed left hemispheres of subjects showing a high degree of overall sulcation (g-SI=1.80) and a low degree of overall sulcation (g-SI=1.46).

Figure 2. Global sulcal index (g-SI) in patients with auditory only (AH, N=17) or patients with audio-visual (A+VH, N=16) hallucinations. Average g-SI in the left and right hemispheres in schizophrenia patients with AH (in blue) or A+VH (in red). Error bars denote the standard error of the mean.

REFERENCES

1. Jardri R, Cachia, A., Thomas, P., Pins, D. *The Neuroscience of hallucinations*. Springer: New-York, 2013.

2. Andreasen NC, Flaum M. Schizophrenia: the characteristic symptoms. *Schizophr Bull* 1991; **17**(1)**:** 27-49.

3. Waters F, Collerton D, Ffytche DH, Jardri R, Pins D, Dudley R *et al.* Visual hallucinations in the psychosis-spectrum, and comparative information from neurodegenerative disorders and eye disease. *Schizophrenia bulletin* In press.

4. Cummings JL, Miller BL. Visual hallucinations. Clinical occurrence and use in differential diagnosis. *The Western journal of medicine* 1987; **146**(1)**:** 46-51.

5. Bracha HS, Wolkowitz OM, Lohr JB, Karson CN, Bigelow LB. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. *Am J Psychiatry* 1989; **146**(4)**:** 526-528.

6. Goodwin DW, Alderson P, Rosenthal R. Clinical significance of hallucinations in psychiatric disorders. A study of 116 hallucinatory patients. *Arch Gen Psychiatry* 1971; **24**(1)**:** 76-80.

7. Mueser KT, Bellack AS, Brady EU. Hallucinations in schizophrenia. *Acta Psychiatr Scand* 1990; **82**(1)**:** 26-29.

8. Frieske DA, Wilson WP. Formal qualities of hallucinations: a comparative study of the visual hallucinations in patients with schizophrenic, organic, and affective psychoses. *Proceedings of the annual meeting of the American Psychopathological Association* 1966; **54:** 49-62.

9. Allen P, Modinos G, Hubl D, Shields G, Cachia A, Jardri R *et al.* Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. *Schizophr Bull* 2012; **38**(4)**:** 695-703.

10. Amad A, Cachia A, Gorwood P, Pins D, Delmaire C, Rolland B *et al.* The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations. *Mol Psychiatry* 2014; **19**(2)**:** 184-191.

11. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry* 2012; **17**(12)**:** 1228-1238.

12. Mangin JF, Jouvent E, Cachia A. In-vivo measurement of cortical morphology: means and meanings. *Curr Opin Neurol* 2010; **23**(4)**:** 359-367.

13. Cachia A, Paillere-Martinot ML, Galinowski A, Januel D, de Beaurepaire R, Bellivier F *et al.* Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. *Neuroimage* 2008; **39**(3)**:** 927-935.

14. Hubl D, Dougoud-Chauvin V, Zeller M, Federspiel A, Boesch C, Strik W *et al.* Structural analysis of Heschl's gyrus in schizophrenia patients with auditory hallucinations. *Neuropsychobiology* 2010; **61**(1)**:** 1-9.

15. Plaze M, Paillere-Martinot ML, Penttila J, Januel D, de Beaurepaire R, Bellivier F *et al.* "Where do auditory hallucinations come from?"--a brain morphometry study of schizophrenia patients with inner or outer space hallucinations. *Schizophr Bull* 2011; **37**(1)**:** 212-221.

16. Lowe GR. The phenomenology of hallucinations as an aid to differential diagnosis. *Br J Psychiatry* 1973; **123**(577)**:** 621-633.

17. Bauer SM, Schanda H, Karakula H, Olajossy-Hilkesberger L, Rudaleviciene P, Okribelashvili N *et al.* Culture and the prevalence of hallucinations in schizophrenia. *Compr Psychiatry* 2011; **52**(3)**:** 319-325.

18. David CN, Greenstein D, Clasen L, Gochman P, Miller R, Tossell JW *et al.* Childhood onset schizophrenia: high rate of visual hallucinations. *J Am Acad Child Adolesc Psychiatry* 2011; **50**(7)**:** 681-686 e683.

19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**(2)**:** 261-276.

20. Andreasen NC. Methods for assessing positive and negative symptoms. *Mod Probl Pharmacopsychiatry* 1990; **24:** 73-88.

21. Duchesnay E, Cachia A, Roche A, Riviere D, Cointepas Y, Papadopoulos-Orfanos D *et al.* Classification based on cortical folding patterns. *IEEE Trans Med Imaging* 2007; **26**(4)**:** 553-565.

22. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry* 2010; **167**(6)**:** 686-693.

23. Penttila J, Paillere-Martinot ML, Martinot JL, Mangin JF, Burke L, Corrigall R *et al.* Global and temporal cortical folding in patients with early-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* 2008; **47**(10)**:** 1125-1132.

24. Gay O, Plaze M, Oppenheim C, Mouchet-Mages S, Gaillard R, Olie JP *et al.* Cortex morphology in first-episode psychosis patients with neurological soft signs. *Schizophr Bull* 2013; **39**(4)**:** 820-829.

25. Penttila J, Cachia A, Martinot JL, Ringuenet D, Wessa M, Houenou J *et al.* Cortical folding difference between patients with early-onset and patients with intermediate-onset bipolar disorder. *Bipolar Disord* 2009; **11**(4)**:** 361-370.

26. Penttila J, Paillere-Martinot ML, Martinot JL, Ringuenet D, Wessa M, Houenou J *et al.* Cortical folding in patients with bipolar disorder or unipolar depression. *J Psychiatry Neurosci* 2009; **34**(2)**:** 127-135.

27. Mangin JF, Riviere D, Cachia A, Duchesnay E, Cointepas Y, Papadopoulos-Orfanos D *et al.* A framework to study the cortical folding patterns. *Neuroimage* 2004; **23 Suppl 1:** S129-138.

28. Zilles K, Armstrong E, Schleicher A, Kretschmann HJ. The human pattern of gyrification in the cerebral cortex. *Anat Embryol (Berl)* 1988; **179**(2)**:** 173-179.

29. Perrot M, Riviere D, Mangin JF. Cortical sulci recognition and spatial normalization. *Med Image Anal* 2011; **15**(4)**:** 529-550.

30. Dubois J, Benders M, Borradori-Tolsa C, Cachia A, Lazeyras F, Ha-Vinh Leuchter R *et al.* Primary cortical folding in the human newborn: an early marker of later functional development. *Brain* 2008; **131**(Pt 8)**:** 2028-2041.

31. Hilgetag CC, Barbas H. Role of mechanical factors in the morphology of the primate cerebral cortex. *PLoS Comput Biol* 2006; **2**(3)**:** e22.

32. Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 1997; **385**(6614)**:** 313-318.

33. Klyachko VA, Stevens CF. Connectivity optimization and the positioning of cortical areas. *Proc Natl Acad Sci U S A* 2003; **100**(13)**:** 7937-7941.

34. Rakic P. Specification of cerebral cortical areas. *Science* 1988; **241**(4862)**:** 170-176.

35. Dehay C, Giroud P, Berland M, Killackey H, Kennedy H. Contribution of thalamic input to the specification of cytoarchitectonic cortical fields in the primate: effects of bilateral enucleation in the fetal monkey on the boundaries, dimensions, and gyrification of striate and extrastriate cortex. *The Journal of comparative neurology* 1996; **367**(1)**:** 70-89.

36. Ford JM, Palzes VA, Roach BJ, Potkin SG, van Erp TG, Turner JA *et al.* Visual Hallucinations Are Associated With Hyperconnectivity Between the Amygdala and Visual Cortex in People With a Diagnosis of Schizophrenia. *Schizophr Bull* 2014.

37. Bombin I, Arango C, Buchanan RW. Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophr Bull* 2005; **31**(4)**:** 962-977.

38. Peralta V, de Jalon EG, Campos MS, Basterra V, Sanchez-Torres A, Cuesta MJ. Risk factors, pre-morbid functioning and episode correlates of neurological soft signs in drug-naive patients with schizophrenia-spectrum disorders. *Psychol Med* 2010**:** 1-11.

39. Biswas P, Malhotra S, Malhotra A, Gupta N. Comparative study of neurological soft signs in schizophrenia with onset in childhood, adolescence and adulthood. *Acta Psychiatr Scand* 2007; **115**(4)**:** 295-303.

40. Vourdas A, Pipe R, Corrigall R, Frangou S. Increased developmental deviance and premorbid dysfunction in early onset schizophrenia. *Schizophr Res* 2003; **62**(1-2)**:** 13-22.

41. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW *et al.* Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci U S A* 2009; **106**(4)**:** 1279-1284.

42. Clos M, Diederen KM, Meijering AL, Sommer IE, Eickhoff SB. Aberrant connectivity of areas for decoding degraded speech in patients with auditory verbal hallucinations. *Brain Struct Funct* 2014; **219**(2)**:** 581-594.

43. Sommer IE, Clos M, Meijering AL, Diederen KM, Eickhoff SB. Resting state functional connectivity in patients with chronic hallucinations. *PLoS ONE* 2012; **7**(9)**:** e43516.

44. Wolf ND, Sambataro F, Vasic N, Frasch K, Schmid M, Schonfeldt-Lecuona C *et al.* Dysconnectivity of multiple resting-state networks in patients with schizophrenia who have persistent auditory verbal hallucinations. *J Psychiatry Neurosci* 2011; **36**(6)**:** 366-374.

45. Jardri R, Thomas P, Delmaire C, Delion P, Pins D. The Neurodynamic Organization of Modality-Dependent Hallucinations. *Cereb Cortex* 2013; **23**(5)**:** 1108-1117.

46. Shine JM, Halliday GM, Naismith SL, Lewis SJ. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? *Mov Disord* 2011; **26**(12)**:** 2154-2159.

47. Ono M, Kubik S, Abarnathey CD. *Atlas of the Cerebral Sulci*. Georg Thieme: New York, 1990.

48. Cachia A, Mangin JF, Riviere D, Papadopoulos-Orfanos D, Kherif F, Bloch I *et al.* A generic framework for the parcellation of the cortical surface into gyri using geodesic Voronoi diagrams. *Med Image Anal* 2003; **7**(4)**:** 403-416.

49. Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron* 2010; **67**(5)**:** 728-734.

50. Ramanan VK, Shen L, Moore JH, Saykin AJ. Pathway analysis of genomic data: concepts, methods, and prospects for future development. *Trends Genet* 2012; **28**(7)**:** 323-332.

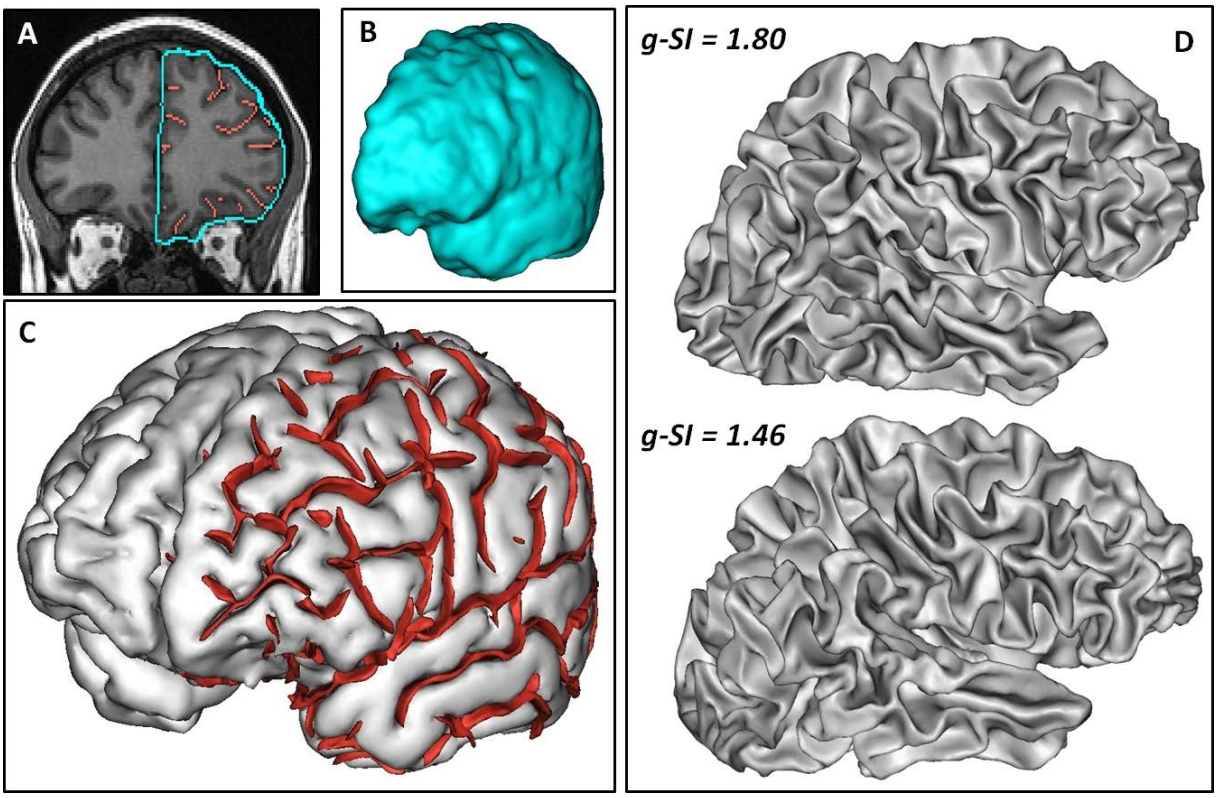


Figure 1

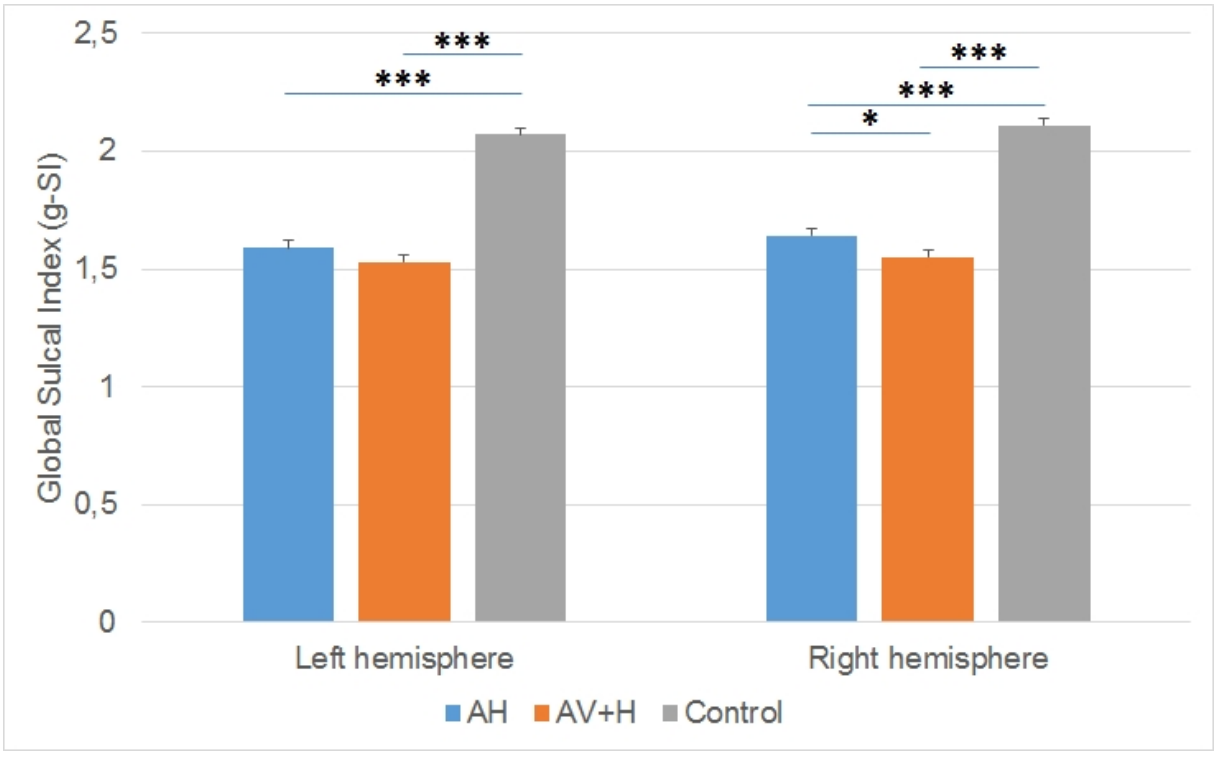


Figure 2

Table 1. Social and clinical characteristics of the study participants. Quantitative (resp. qualitative) demographic and clinical characteristics comparisons between patients with auditory hallucinations (AH) and patients with audio-visual hallucinations (A+VH) were based on bilateral Student T (resp. Chi-2) tests.

	Healthy Controls (HC)	**Patients with auditory hallucinations (AH)**	**Patients with audio-visual hallucinations (A+VH)**	**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 ± SD)	29.93 ± 5.2	30.47 ± 8.7	30.44 ± 12.6	0.9
PANSS score				
Total (mean ± SD)	—	79.71 ± 21.8	75.64 ± 18.45	0.6
Positive (mean ± SD)	—	19.6 ± 5.1	22.7 ± 4.9	0.1
Negative (mean ± SD)	—	21.29 ± 7.5	17.6 ± 6.5	0.2
General (mean ± SD)	—	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 ± SD)	—	4.7 ±0.6	4.8 ±0.5	0.9
Item 6 (mean ± SD)	—	0	4.5 ±0.5	< 0.0001
Olanzapine equivalent dose (mean ± SD)	—	23.7 ± 7.8	20.57 ± 15.0	0.4

Table 2. Results of g-SI and global volumes analyses. Data are presented as means (standard error of the mean). Variables significantly different between patients with patients with auditory hallucinations (AH) and patients with audio-visual hallucinations (A+VH) are indicated by bold font (patients with auditory hallucinations (AH) as reference). All results were linearly adjusted for age and gender. [*GM: Grey Matter; WM: White Matter; CSF: Cerebro-Spinal Fluid*]

	HC	**AH**	**A+VH**		**A+VH versus AH**		
Left Hemisphere	mean (SD)				Difference, %	*F*	*p* value
Global Sulcal Index (g-SI)	2.07 (0.03)	1.59 (0.03)	1.53 (0.03)		-3,77	2.39	0.13
Normalised GM volume, %	46.65 (0.88)	45.66 (0.92)	45.20 (0.91)		-1,01	0.11	0.73
Normalised WM volume, %	38.83 (0.59)	38.62 (0.59)	39.52 (0.60)		2,33	1.35	0.25
Normalised CSF volume, %	14.51 (0.72)	15.70 (0.72)	15.27 (0.74)		-2,74	0.15	0.7
Right Hemisphere							
Global Sulcal Index (g-SI)	**2.11 (0.03)**	**1.64 (0.03)**	**1.55 (0.03)**		**-5,49**	**5.10**	**0.03**
Normalised GM volume, %	46.78 (0.85)	45.90 (0.85)	45.51 (0.88)		-0,85	0.09	0.77
Normalised WM volume, %	38.72 (0.60)	38.61 (0.60)	39.19 (0.62)		1,50	0.50	0.48
Normalised CSF volume, %	14.50 (0.70)	15.48 (0.70)	15.29 (0.72)		-1,23	0.02	0.86

INTERVENTIONS THÉRAPEUTIQUES CENTRÉES SUR LA NEUROPLASTICITÉ : L'EXEMPLE DE LA NEUROMODULATION

Welcome to Cerebro.

Charles Xavier

Du point de vue de la NP, l'objectif du traitement des troubles psychiatriques est d'augmenter ou d'améliorer cette plasticité permettant de modifier les circuits neuronaux pathologiques associés au trouble. Les traitements des troubles psychiatriques qu'ils soient pharmacologiques (Martinowich and Lu, 2007) et psychothérapeutiques (Collerton, 2013) sont donc logiquement très étroitement associés à la NP. Cette partie ne décrira que les interventions thérapeutiques centrées sur la NP faisant intervenir des méthodes de neuromodulation.

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 et al., 2013a). La neuromodulation est devenue une alternative prometteuse dans la prise en charge thérapeutique des troubles psychiatriques de façon générale mais également dans des situations de résistance au traitement conventionnel. La neuromodulation s'appuie actuellement sur plusieurs techniques, décrites ci-dessous, permettant de stimuler la NP.

5.1. La stimulation magnétique transcrânienne

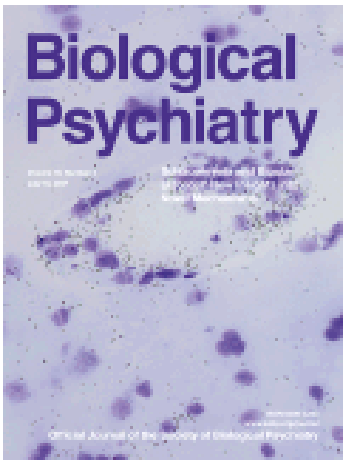
La stimulation magnétique transcrânienne répétée (notée rTMS pour *repetitive Transcranial Magnetic Stimulation)* est une technique permettant de réaliser, de manière non invasive et indolore chez l'Homme, une stimulation cérébrale focalisée au travers du crâne. La rTMS dérive du principe décrit par Faraday au XIX^{ème} siècle : tout champ électrique oscillant est associé à un champ magnétique oscillant perpendiculaire et se déplaçant dans la même direction, et *vice versa*. En 1985, l'équipe d'Anthony Barker de Sheffield obtint la contraction musculaire des mains par stimulation magnétique non douloureuse d'un sujet. Ces expériences constituent le point de départ de l'application en psychiatrie de la TMS (Micoulaud-Franchi et al., 2013b).

Grâce à ses propriétés de modification de l'excitabilité corticale, la rTMS est apparue, depuis une quinzaine d'années, comme une avancée majeure dans le traitement des pathologies où sont révélées des zones cérébrales dysfonctionnelles. Le système permet de générer un champ magnétique de manière intermittente par le passage d'un courant électrique dans une bobine qui peut ensuite facilement pénétrer les tissus de surface. La variation rapide du champ magnétique obtenue produit un flux de courant dans les tissus cérébraux sous-jacents, responsable d'une dépolarisation membranaire au niveau axonal et d'une activation neurale (Hallett, 2000). Quand elle est utilisée à visée thérapeutique, la rTMS est délivrée de manière répétée sous la forme de sessions quotidiennes pendant plusieurs jours, voire semaines.

La rTMS est devenue une alternative prometteuse dans la prise en charge thérapeutique des troubles psychiatriques mais aussi dans des situations de résistance au traitement conventionnel. Par exemple, chez 25 à 30% des patients souffrant de schizophrénie les hallucinations acoustico-verbales (HAV) peuvent persister malgré un traitement antipsychotique bien conduit (Shergill et al., 1998). Chez ces patients, l'utilisation de la rTMS permet ainsi de réduire l'excitabilité corticale des régions retrouvées anarchiquement activées dans les hallucinations en imagerie cérébrale. Une méta-analyse récente, prenant en compte le biais de publication, a permis de confirmer l'efficacité de ce traitement dans cette indication (**Article 7**).

Le mécanisme d'action de la rTMS implique des mécanismes neuroplastiques. Il a par exemple été montré des modifications de connectivité fonctionnelle après stimulation au niveau de la jonction temporo-pariétale (une région cible choisie pour son implication dans les hallucinations auditives) (Hoffman et al., 2007; Vercammen et al., 2010). La rTMS, dans la prise en charge des hallucinations résistantes, peut également être optimisée, notamment par la modulation de la force de connexion de réseaux neuronaux spécifiques repérés en imagerie fonctionnelle (Jardri et al., 2009).

ARTICLE 7



What is the real effect of 1-hz repetitive transcranial magnetic stimulation on hallucinations? Controlling for publication bias in neuromodulation trials

Morgane DEMEULEMEESTER, Ali AMAD, Maxime BUBROVSZKY, Delphine PINS, Pierre THOMAS,

Renaud JARDRI

Biological Psychiatry 2012;71:e15–e16

5.2. La stimulation transcrânienne par courant direct

Une autre méthode de neuromodulation semble particulièrement intéressante dans la prise en charge des hallucinations résistantes, il s'agit de la stimulation transcrânienne par courant direct (noté tDCS pour *transcranial Direct Current Stimulation*).

Cette méthode a particulièrement été étudiée en psychiatrie en Russie dans les années 1940 et les premiers essais cliniques contrôlés ont été réalisés par l'équipe de Walter Paulus en Allemagne durant la fin des années 1990. La tDCS délivre un courant électrique continu de faible intensité entre une anode et une cathode posées sur le scalp. L'effet sur le niveau d'activité cérébrale dépend de la polarité des électrodes : un effet activateur (dépolarisant) est obtenu sous l'anode (positive) et un effet inhibiteur (hyperpolarisant) sous la cathode (négative) (Micoulaud-Franchi et al., 2013b). Cette méthode permet de cibler deux régions corticales de façon concomitante et d'avoir un effet plus durable sur l'excitabilité corticale (Nitsche and Paulus, 2000). La tDCS est un outil de stimulation facile à utiliser, avec très peu d'effets secondaires et permettant des modèles expérimentaux en double insu contrôlé par placebo grâce à ses des modalités de programmation (Vernay et al., 2012).

La tDCS a récemment été utilisée dans le traitement des HAV résistantes chez des patients souffrant de schizophrénie. En effet, les HAV sont associées à une hypoactivité du cortex préfrontal et hyperactivité du cortex temporo-pariétal gauche (Lawrie et al., 2002). Le traitement par tDCS en appliquant l'anode excitatrice en regard du cortex préfrontal parallèlement à la cathode inhibitrice en regard du cortex temporo-pariétal gauche a permis, dans une étude tDCS contre placebo de 30 patients, une diminution importante des HAV résistantes (en moyenne diminution de 30 %). Le protocole consistait en 2 séances de 20 minutes de tDCS par jour pendant 5 jours consécutifs (Brunelin et al., 2012).

5.3. L’électro-convulsivothérapie

L’électro-convulsivothérapie (ECT) consiste à provoquer une crise convulsive par l'application d'une stimulation électrique biphasique à travers des électrodes placées sur le scalp. L'ECT apparaît en avril 1938 avec Ugo Cerletti et Lucio Bini. Cerletti est guidé par l’idée que les crises épileptiques sont un facteur protecteur pour les troubles psychiatriques, notamment la schizophrénie (Micoulaud-Franchi et al., 2013b). Depuis, de très nombreux progrès ont été réalisés dans la mise en place de l'ECT au niveau de l'anesthésie, de la prise en charge de la douleur, ainsi que différents protocoles de stimulation électrique permettant d'améliorer l'efficacité de la technique tout en minimisant les effets secondaires.

L'ECT est actuellement le traitement antidépresseur le plus efficace et est indiqué dans la prise en charge de la dépression résistante aux traitements pharmacologiques et psychothérapeutiques (Rosa and Lisanby, 2012). La dépression est associée à une diminution de la NP marquée par une diminution des facteurs trophiques cérébraux, une réduction de la neurogenèse, une diminution de connexion entre les neurones de l'hippocampe et du cortex préfrontal et une diminution du volume de ces structures proportionnelle au nombre d'épisodes dépressifs (Player et al., 2013).

Même si son mécanisme d'action n'est pas entièrement élucidé, l'effet antidépresseur de l'ECT stimule la NP (Holtzmann et al., 2007). En effet, l'ECT a été associé à une augmentation des concentrations de facteurs neurotrophiques (ex: BDNF, NGF, etc.), une croissance cellulaire accélérée, une augmentation des connexions synaptiques et à des modifications de la concentration de certaines hormones et neuropeptides (Wahlund and von Rosen, 2003).

5.4. Stimulation cérébrale profonde

Comme la TMS et la tDCS, la stimulation cérébrale profonde (notée DBS pour *Deep Brain Stimulation*) utilise une stimulation électrique pour stimuler la NP et produire des changements comportementaux. La différence avec la DBS est que le courant est délivré à travers des électrodes implantées dans le cerveau, dont les paramètres de stimulation (fréquence, intensité…) peuvent être programmés et optimisés. Les principaux effets secondaires de cette technique sont ceux liés à l'intervention chirurgicale (Szekely and Polosan, 2010).

La DBS a initialement été développée en neurologie, notamment dans la maladie de Parkinson, et a ensuite été développée dans des troubles psychiatriques résistants comme les troubles obsessionnels compulsifs avec des résultats très prometteurs (Mallet et al., 2008).

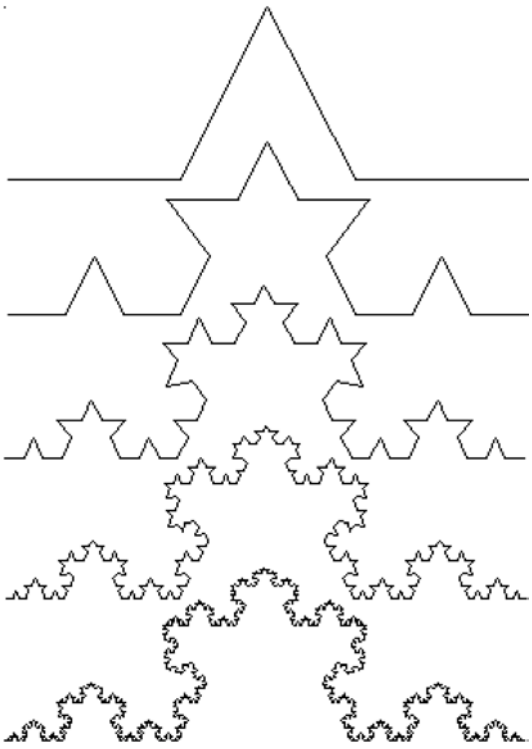
Les mécanismes qui sous-tendent l'efficacité thérapeutique de la DBS ne sont pas entièrement élucidés mais semblent impliquer des modifications neuroplastiques intenses et durables (Lujan et al., 2008).

CONCLUSION ET PERSPECTIVES

L'environnement ne contient pas d'attributs, c'est l'histoire, récurrente, cyclique qui fait émerger les attributs du monde.

Francisco Varela

Small is beautiful, more is different.



Les objectifs de ce travail de thèse étaient d'une part de montrer que la NP permettait une meilleure compréhension de la physiopathologie des troubles psychiatriques et d'améliorer les traitements de ces troubles et d'autre part de montrer que la grande diversité des troubles psychiatriques, et ceci à tous les niveaux, pouvait, sous l'angle de la NP, être considérée comme un avantage.

L'étude de l'implication de la NP dans les troubles psychiatriques peut également s'observer à plusieurs échelles (du moléculaire au comportemental) et la recherche dans ce domaine doit maintenant être réalisée de façon translationnelle grâce à des approches collaboratives incluant des chercheurs fondamentaux et cliniques. En effet, le concept de NP réunit dans un même système plusieurs acteurs apparemment éloignés et ayant des actions à des échelles microscopiques et macroscopique parfois difficiles à associer (DeFelipe, 2010). De plus, tous les acteurs du système nerveux sont impliqués dans la régulation de la NP : les gènes, tous les neurotransmetteurs, la substance grise et blanche, et la NP est impliquée dans les comportements normaux (mémoire, processus automatiques) et pathologiques, allant de la schizophrénie aux troubles de personnalité.

Nous pensons qu'un changement de paradigme épistémologique centré sur la NP permettrait de nouveaux développements dans la compréhension et le traitement des troubles psychiatriques. En neurosciences, et dans les sciences biomédicales en général, l'approche épistémologique actuelle est qualifiée de « réductionniste ». Cette approche héritée du deuxième précepte de Descartes (Descartes, 1637) réduit un système complexe en sous-partie plus simple à comprendre. Cette approche a effectivement été à l'origine de nombreuses découvertes et avancées scientifiques et médicales.

Cependant, les limites de cette méthode pourraient commencer à être atteintes (Ahn et al., 2006). En effet, les neurosciences, mais également les autres disciplines biomédicales, accumulent des quantités astronomiques de résultats d'expérience, de données d'imagerie, de génétique, de biologie, de neuropsychologie, sans pour autant faire le lien entre les différents aspects d'un phénomène étudié, et sans proposer d'approche globale. Nous pouvons illustrer ce propos avec l'exemple de la recherche en génétique. Lors de la mise en place du projet de séquençage complet du génome humain, D. Koshland expliquait dans l'éditorial de la revue *Science* que cela aller permettre de comprendre au maximum : le tout de la nature humaine, et au minimum : l'essentiel des mécanismes de survenue des maladies (Koshland, 1989).

Une autre approche, évoquant les limites du réductionnisme, se développe depuis maintenant plusieurs années. Il s'agit d'une approche globale qualifiée de science de la complexité. De nombreuses définitions de la complexité existent, mais classiquement un système est dit complexe quand ses propriétés ne sont pas entièrement expliquées par la compréhension de ses parties (Gallagher and Appenzeller, 1999). Ainsi, la complexité s'intéresse aux relations entre le tout et ses parties, et au caractère holistique d'un problème. La complexité comporte certaines propriétés comme l'émergence, l'auto-organisation, la robustesse… et s'aide d'outils mathématiques, informatiques et computationnels. En neurosciences la NP, grâce à son caractère global, ses nombreux acteurs biologiques et ses liens avec l'environnement, nous semble être une approche intéressante du point de vue de la science des systèmes complexes (Kotaleski and Blackwell, 2010). Il pourrait ainsi être intéressant d'aborder le concept de NP sous l'angle de la complexité, ce qui pourrait nous permettre de mieux appréhender la manière dont l'environnement modifie le tissu cérébral.

Cette approche globale et novatrice permettrait une meilleure compréhension des troubles neuropsychiatriques et d'imaginer de nouvelles stratégies thérapeutiques notamment grâce à des études couplant différentes techniques comme la génétique, l'épigénétique et l'imagerie cérébrale, ainsi que des outils mathématiques, informatiques et computationnels inspirés du champ des systèmes complexes. Ces approches intégrées commencent à se développer aujourd'hui et nous semblent constituer les véritables enjeux de la recherche en neurosciences et en psychiatrie aujourd'hui.

Ainsi, du fait de leur prévalence importante, de leur sévérité et de la morbi-mortalité associée, les troubles psychiatriques devraient représenter une priorité urgente de santé publiques (Buka, 2008; Whiteford et al., 2013). Certains chercheurs ont alors appelés, et ceci dans des revues scientifiques prestigieuses, à de nouvelles approches permettant une meilleure compréhension des troubles et de leurs causes pour améliorer la santé des populations (Akil et al., 2010). Il a été proposé que l'étude de la NP permettrait une meilleure compréhension de la physiopathologie des troubles psychiatriques et d'améliorer leurs traitements (Cramer et al., 2011).

Nous proposons que la NP, mécanisme essentiel pour le traitement des troubles psychiatriques, a également une grande influence sur la pathogenèse de ces troubles que l'on peut décrire comme un phénomène étant impliqué dans **l'adaptation à la pathologie**. Certains de nos résultats peuvent d'ailleurs tout à fait être interprétés dans ce sens. Par exemple, nous avons mis en évidence que l'hippocampe joue un rôle spécifique chez les patients souffrant de schizophrénie et présentant des hallucinations visuelles et que cette structure est hypertrophiée chez les patients avec des hallucinations visuelles. L'hippocampe étant capable de modifications plastiques et son volume augmentant au plus il est sollicité, ces résultats vont dans le sens d'une adaptation plastique aux hallucinations visuelles.

L’adaptation à la pathologie est un concept tout à fait pertinent dans le cadre des troubles psychiatriques. De façon générale, les troubles psychiatriques sont marqués, et ce en dehors du trouble obsessionnel compulsif, par leur évolution souvent chronique, la répétition de leurs symptômes (ex : cf. **Article 1**) et de leurs épisodes (ex: épisodes dépressifs, épisodes psychotiques). De façon intéressante, la répétition de processus cognitifs est associée à des patterns caractéristiques de connectivité cortico-sous-corticale, impliquant les ganglions de la base, ainsi que des gènes impliqués dans la régulation de la NP (Smith and Graybiel, 2014).

Ces perspectives seront abordées dans le cadre de mon projet de post-doctorat dont l’objectif de **rechercher des patterns communs aux troubles psychiatriques liés à l'adaptation à la pathologie plutôt qu'à la physiopathologie d'un trouble psychiatrique *per se***. Cette approche se veut ainsi **transdiagnostique**, puisque notre hypothèse est qu'il existe des patterns communs de régulation plastique entre les différents troubles psychiatriques, et **translationnelle** puisqu'au niveau méthodologique, différents niveaux seront analysés notamment génétique et en neuroimagerie.

D'un point de vue méthodologique, les méthodes complexes de "*machine learning*" et de reconnaissance de patterns seront utilisés (**Cf. Figure 5**). Ces méthodes bio-informatiques permettent en effet de rechercher dans de larges banques de données, des points communs et des différences entre les sujets permettant de définir des groupes. Ces méthodes peuvent s'appliquer à des données d'imagerie et de génétique. Ce projet sera réalisé au *Centre for Neuroimaging Science*s (CNS) à l'*Institut of Psychiatry* (IoP, King's College, London) dirigé par le Pr. Steven Williams.

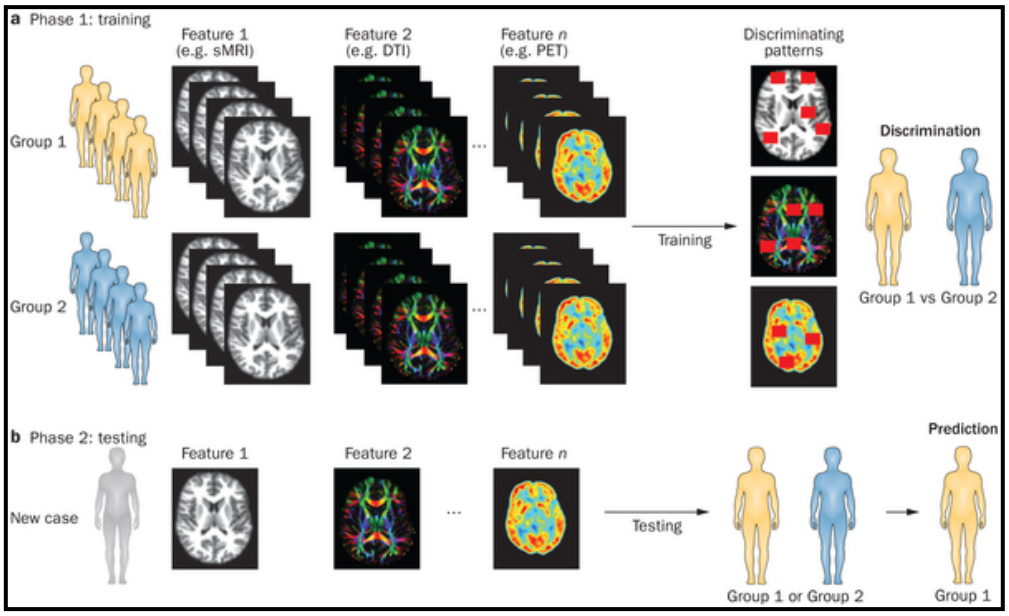


Figure 5: Exemple de classification multivariée (Ecker and Murphy, 2014). Dans la phase d'entraînement, un algorithme est développé pour différencier des groupes (ex: patients vs contrôles). Dans la phase de test, l'algorithme est utilisé pour déterminer dans quel groupe classer de nouvelles observations.

Les perspectives de ce travail sont **thérapeutiques**. En effet, cette approche permettrait de faire la différence entre les conséquences liées à l'adaptation plastique à la pathologie plutôt qu'à la pathologie elle-même et donc permettra de mieux cibler les traitements en distinguant les traitements symptomatiques et étiologiques. Cette approche présente également des **perspectives fondamentales** puisque le couplage génétique et imagerie en "*machine learning*" et reconnaissance de pattern représente une innovation méthodologique.

RÉFÉRENCES

Ahn, A.C., Tewari, M., Poon, C.-S., Phillips, R.S., 2006. The limits of reductionism in medicine: could systems biology offer an alternative? PLoS Med. 3, e208. doi:10.1371/journal.pmed.0030208

Akil, H., Brenner, S., Kandel, E., Kendler, K.S., King, M.C., Scolnick, E., Watson, J.D., Zoghbi, H.Y., 2010. The Future of Psychiatric Research: Genomes and Neural Circuits. Science 327, 1580–1581. doi:10.1126/science.1188654

Akiskal, H.S., 1981. Subaffective disorders: dysthymic, cyclothymic and bipolar II disorders in the "borderline" realm. Psychiatr. Clin. North Am. 4, 25–46.

Allen, P., Modinos, G., Hubl, D., Shields, G., Cachia, A., Jardri, R., Thomas, P., Woodward, T., Shotbolt, P., Plaze, M., Hoffman, R., 2012. Neuroimaging Auditory Hallucinations in Schizophrenia: From Neuroanatomy to Neurochemistry and Beyond. Schizophr. Bull. doi:10.1093/schbul/sbs066

Amad, A., Geoffroy, P.A., Vaiva, G., Thomas, P., 2013. [Personality and personality disorders in the elderly: diagnostic, course and management]. L'Encéphale 39, 374–382. doi:10.1016/j.encep.2012.08.006

Andreasen, N.C., Flaum, M., 1991. Schizophrenia: The Characteristic Symptoms. Schizophr. Bull. 17, 27 –49. doi:10.1093/schbul/17.1.27

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R., 2009. Vulnerability genes or plasticity genes. Mol Psychiatry 14, 746–754.

Bergeret, J., Bécache, A., Boulanger, J.-J., Chartier, J.-P., 2004. Psychologie pathologique: Théorique et clinique, 9e ed. Editions Masson.

Berlucchi, G., Buchtel, H.A., 2009. Neuronal plasticity: historical roots and evolution of meaning. Exp. Brain Res. 192, 307–319. doi:10.1007/s00221-008-1611-6

Bernstein, Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., Ruggiero, J., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 151, 1132–1136.

Berrios, G.E., Luque, R., Villagrán, J.M., 2003. Schizophrenia: A Conceptual History. Int. J. Psychol. Psychol. Ther. 3, 111–140.

Binder, E.B., Bradley, R.G., Liu, W., Epstein, M.P., Deveau, T.C., Mercer, K.B., Tang, Y., Gillespie, C.F., Heim, C.M., Nemeroff, C.B., Schwartz, A.C., Cubells, J.F., Ressler, K.J., 2008. Association of FKBP5 Polymorphisms and Childhood Abuse With Risk of Posttraumatic Stress Disorder Symptoms in Adults. JAMA 299, 1291–1305. doi:10.1001/jama.299.11.1291

Bouvard, M., Fontaine-Buffe, M., Cungi, C., Adeleine, P., Chapoutier, C., Durafour, E., Bouchard, C., Cottraux, J., 1999. [Preliminary studies of the structured diagnostic interview for personality disorders: SCID II]. L'Encéphale 25, 416–421.

Bracha, H.S., Wolkowitz, O.M., Lohr, J.B., Karson, C.N., Bigelow, L.B., 1989. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. Am. J. Psychiatry 146, 526–528.

Brennand, K.J., Simone, A., Jou, J., Gelboin-Burkhart, C., Tran, N., Sangar, S., Li, Y., Mu, Y., Chen, G., Yu, D., McCarthy, S., Sebat, J., Gage, F.H., 2011. Modelling schizophrenia using human induced pluripotent stem cells. Nature 473, 221–225. doi:10.1038/nature09915

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M.-F., Saoud, M., Mechri, A., Poulet, E., 2012. Examining Transcranial Direct-Current Stimulation (tDCS) as a Treatment for Hallucinations in Schizophrenia. Am. J. Psychiatry 169, 719–724. doi:10.1176/appi.ajp.2012.11071091

Buka, S.L., 2008. Psychiatric Epidemiology: Reducing the Global Burden of Mental Illness. Am. J. Epidemiol. 168, 977–979. doi:10.1093/aje/kwn298

Burmeister, M., McInnis, M.G., Zöllner, S., 2008. Psychiatric genetics: progress amid controversy. Nat. Rev. Genet. 9, 527–540. doi:10.1038/nrg2381

Callicott, J.H., Straub, R.E., Pezawas, L., Egan, M.F., Mattay, V.S., Hariri, A.R., Verchinski, B.A., Meyer-Lindenberg, A., Balkissoon, R., Kolachana, B., Goldberg, T.E., Weinberger, D.R., 2005. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 102, 8627–8632. doi:10.1073/pnas.0500515102

Canli, T., Lesch, K.-P., 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. Nat. Neurosci. 10, 1103–1109. doi:10.1038/nn1964

Cannon, T.D., Hennah, W., van Erp, T.G.M., Thompson, P.M., Lonnqvist, J., Huttunen, M., Gasperoni, T., Tuulio-Henriksson, A., Pirkola, T., Toga, A.W., Kaprio, J., Mazziotta, J., Peltonen, L., 2005. Association of DISC1/TRAX Haplotypes With Schizophrenia, Reduced Prefrontal Gray Matter, and Impaired Short- and Long-term Memory. Arch Gen Psychiatry 62, 1205–1213. doi: 10.1001/archpsyc.62.11.1205

Caspi, A., Hariri, A.R., Holmes, A., Uher, R., Moffitt, T.E., 2010. Genetic Sensitivity to the Environment: The Case of the Serotonin Transporter Gene and Its Implications for Studying Complex Diseases and Traits. Am. J. Psychiatry 167, 509–527. doi:10.1176/appi.ajp.2010.09101452

Collerton, D., 2013. Psychotherapy and brain plasticity. Front. Psychol. 4. doi:10.3389/fpsyg.2013.00548

Cramer, S.C., Sur, M., Dobkin, B.H., O'Brien, C., Sanger, T.D., Trojanowski, J.Q., Rumsey, J.M., Hicks, R., Cameron, J., Chen, D., Chen, W.G., Cohen, L.G., deCharms, C., Duffy, C.J., Eden, G.F., Fetz, E.E., Filart, R., Freund, M., Grant, S.J., Haber, S., Kalivas, P.W., Kolb, B., Kramer, A.F., Lynch, M., Mayberg, H.S., McQuillen, P.S., Nitkin, R., Pascual-Leone, A., Reuter-Lorenz, P., Schiff, N., Sharma, A., Shekim, L., Stryker, M., Sullivan, E.V., Vinogradov, S., 2011. Harnessing neuroplasticity for clinical applications. Brain 134, 1591–1609. doi:10.1093/brain/awr039

Cutting, J., 1990. The Right Cerebral Hemisphere and Psychiatric Disorders, First Edition. ed. Oxford University Press, USA.

Cutting, J., Dunne, F., 1989. Subjective Experience of Schizophrenia. Schizophr. Bull. 15, 217 –231. doi:10.1093/schbul/15.2.217

De Moor, M.H.M., Distel, M.A., Trull, T.J., Boomsma, D.I., 2009. Assessment of borderline personality features in population samples: is the Personality Assessment Inventory-Borderline Features scale measurement invariant across sex and age? Psychol. Assess. 21, 125–130. doi:10.1037/a0014502

DeFelipe, J., 2010. From the Connectome to the Synaptome: An Epic Love Story. Science 330, 1198 – 1201. doi:10.1126/science.1193378

Descartes, R., 1637. Discours de la méthode: pour bien conduire sa raison, et chercher la vérité dans les sciences.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., May, A., 2004. Neuroplasticity: changes in grey matter induced by training. Nature 427, 311–312. doi:10.1038/427311a

Ecker, C., Murphy, D., 2014. Neuroimaging in autism—from basic science to translational research. Nat. Rev. Neurol. 10, 82–91. doi:10.1038/nrneurol.2013.276

Ekelund, J., Hennah, W., Hiekkalinna, T., Parker, A., Meyer, J., Lönnqvist, J., Peltonen, L., 2004. Replication of 1q42 linkage in Finnish schizophrenia pedigrees. Mol. Psychiatry 9, 1037–1041. doi:10.1038/sj.mp.4001536

Ford, J.M., Mathalon, D.H., Whitfield, S., Faustman, W.O., Roth, W.T., 2002. Reduced communication between frontal and temporal lobes during talking in schizophrenia. Biol. Psychiatry 51, 485–492. doi:16/S0006-3223(01)01335-X

Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 30, 115–125. doi:16/S0920-9964(97)00140-0

Friston, K.J., Frith, C.D., Fletcher, P., Liddle, P.F., Frackowiak, R.S., 1996. Functional topography: multidimensional scaling and functional connectivity in the brain. Cereb. Cortex N. Y. N 1991 6, 156–164.

Frith, C.D., Friston, K.J., Herold, S., Silbersweig, D., Fletcher, P., Cahill, C., Dolan, R.J., Frackowiak, R.S., Liddle, P.F., 1995. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. Br. J. Psychiatry J. Ment. Sci. 167, 343–349.

Gallagher, R., Appenzeller, T., 1999. Beyond Reductionism. Science 284, 79. doi:10.1126/science.284.5411.79

Ge, T., Schumann, G., Feng, J., 2013. Imaging genetics — towards discovery neuroscience. Quant. Biol. 1, 227–245. doi:10.1007/s40484-013-0023-1

Griffiths, A.J.F., Miller, J.H., Suzuki, D.T., Lewontin, R.C., Gelbart, W.M., 2002. Introduction à l'analyse génétique. De Boeck Supérieur.

Grinker, R.R., Werble, B., Drye, R.C., 1968. The borderline syndrome: a behavioral study of egofunctions. Basic Books.

Gunderson, J.G., 2009. Borderline personality disorder: ontogeny of a diagnosis. Am. J. Psychiatry 166, 530–539. doi:10.1176/appi.ajp.2009.08121825

Hallett, M., 2000. Transcranial magnetic stimulation and the human brain. Nature 406, 147–150. doi:10.1038/35018000

Herman, J.L., Perry, J.C., van der Kolk, B.A., 1989. Childhood trauma in borderline personality disorder. Am. J. Psychiatry 146, 490–495.

Hodgkinson, C.A., Goldman, D., Jaeger, J., Persaud, S., Kane, J.M., Lipsky, R.H., Malhotra, A.K., 2004. Disrupted in schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. Am. J. Hum. Genet. 75, 862–872. doi:10.1086/425586

Hoffman, R.E., Buchsbaum, M.S., Escobar, M.D., Makuch, R.W., Nuechterlein, K.H., Guich, S.M., 1991. EEG coherence of prefrontal areas in normal and schizophrenic males during perceptual activation. J. Neuropsychiatry Clin. Neurosci. 3, 169–175.

Hoffman, R.E., Hampson, M., Wu, K., Anderson, A.W., Gore, J.C., Buchanan, R.J., Constable, R.T., Hawkins, K.A., Sahay, N., Krystal, J.H., 2007. Probing the Pathophysiology of Auditory/Verbal Hallucinations by Combining Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation. Cereb. Cortex 17, 2733 –2743. doi:10.1093/cercor/bhl183

Holtzmann, J., Polosan, M., Baro, P., Bougerol, T., 2007. ECT : de la neuroplasticité aux mécanismes d'action. L'Encéphale 33, 572–578. doi:10.1016/S0013-7006(07)92055-2

Homberg, J.R., Lesch, K.-P., 2011. Looking on the Bright Side of Serotonin Transporter Gene Variation. Biol. Psychiatry 69, 513–519. doi:10.1016/j.biopsych.2010.09.024

Hua, J.Y., Smith, S.J., 2004. Neural activity and the dynamics of central nervous system development. Nat. Neurosci. 7, 327–332. doi:10.1038/nn1218

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., Maier, S.E., Schroth, G., Lovblad, K., Dierks, T., 2004. Pathways That Make Voices: White Matter Changes in Auditory Hallucinations. Arch Gen Psychiatry 61, 658–668. doi:10.1001/archpsyc.61.7.658

Hulak, F., 2000. La dissociation, de la séjonction à la division du sujet: Genèse et évolution d'un concept. LÉvolution Psychiatr. 65, 19–30. doi:16/S0014-3855(00)88874-X

Jardri, R., Pins, D., Bubrovszky, M., Lucas, B., Lethuc, V., Delmaire, C., Vantyghem, V., Despretz, P., Thomas, P., 2009. Neural functional organization of hallucinations in schizophrenia: Multisensory dissolution of pathological emergence in consciousness. Conscious. Cogn. 18, 449–457. doi:10.1016/j.concog.2008.12.009

Kernberg, O., 1967. Borderline Personality Organization. J Amer Psychoanal Assn 15, 641–685.

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J.C., Pariante, C.M., Pace, T.W.W., Mercer, K.B., Mayberg, H.S., Bradley, B., Nemeroff, C.B., Holsboer, F., Heim, C.M., Ressler, K.J., Rein, T., Binder, E.B., 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat. Neurosci. 16, 33–41. doi:10.1038/nn.3275

Knight, R.P., 1953. Borderline states. Bull. Menninger Clin. 17, 1–12.

Knudsen, E.I., 2004. Sensitive periods in the development of the brain and behavior. J. Cogn. Neurosci. 16, 1412–1425. doi:10.1162/0898929042304796

Kolb, B., Gibb, R., 2011. Brain plasticity and behaviour in the developing brain. J. Can. Acad. Child Adolesc. Psychiatry J. Académie Can. Psychiatr. Enfant Adolesc. 20, 265–276.

Koshland, D.E., Jr, 1989. Sequences and consequences of the human genome. Science 246, 189.

Kotaleski, J.H., Blackwell, K.T., 2010. Modelling the molecular mechanisms of synaptic plasticity using systems biology approaches. Nat. Rev. Neurosci. 11, 239–251.

Lawrie, S.M., Buechel, C., Whalley, H.C., Frith, C.D., Friston, K.J., Johnstone, E.C., 2002. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biol. Psychiatry 51, 1008–1011. doi:10.1016/S0006-3223(02)01316-1

Le Roux, A., Benattar, B., Van Amerongen, P., Hanon, C., Pascal, J.C., 2004. À propos du syndrome d'Ekbom. Ann. Méd.-Psychol. Rev. Psychiatr. 162, 755–761. doi:16/j.amp.2004.08.010

Le Strat, Y., Ramoz, N., Gorwood, P., 2009. The role of genes involved in neuroplasticity and neurogenesis in the observation of a gene-environment interaction (GxE) in schizophrenia. Curr. Mol. Med. 9, 506–518.

Leichsenring, F., Leibing, E., Kruse, J., New, A.S., Leweke, F., 2011. Borderline personality disorder. The Lancet 377, 74–84. doi:10.1016/S0140-6736(10)61422-5

Lenzenweger, M.F., 2008. Epidemiology of personality disorders. Psychiatr. Clin. North Am. 31, 395–403, vi. doi:10.1016/j.psc.2008.03.003

Lewis, K.L., Grenyer, B.F.S., 2009. Borderline personality or complex posttraumatic stress disorder? An update on the controversy. Harv. Rev. Psychiatry 17, 322–328. doi:10.3109/10673220903271848

Lieb, K., Vollm, B., Rucker, G., Timmer, A., Stoffers, J.M., 2010. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br. J. Psychiatry 196, 4–12. doi:10.1192/bjp.bp.108.062984

Lieb, K., Zanarini, M.C., Schmahl, C., Linehan, M.M., Bohus, M., 2004. Borderline personality disorder. The Lancet 364, 453–461. doi:10.1016/S0140-6736(04)16770-6

Linehan, M.M., 1987. Dialectical behavior therapy for borderline personality disorder. Theory and method. Bull. Menninger Clin. 51, 261–276.

Loranger, A.W., Oldham, J.M., Tulis, E.H., 1982. Familial transmission of DSM-III borderline personality disorder. Arch. Gen. Psychiatry 39, 795–799.

Lujan, J.L., Chaturvedi, A., McIntyre, C.C., 2008. Tracking the mechanisms of deep brain stimulation for neuropsychiatric disorders. Front. Biosci. J. Virtual Libr. 13, 5892.

Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., Frith, C.D., 2000. Navigation-related structural change in the hippocampi of taxi drivers. Proc. Natl. Acad. Sci. U. S. A. 97, 4398–4403. doi:10.1073/pnas.070039597

Mallet, L., Polosan, M., Jaafari, N., Baup, N., Welter, M.-L., Fontaine, D., du Montcel, S.T., Yelnik, J., Chéreau, I., Arbus, C., Raoul, S., Aouizerate, B., Damier, P., Chabardès, S., Czernecki, V., Ardouin, C., Krebs, M.-O., Bardinet, E., Chaynes, P., Burbaud, P., Cornu, P., Derost, P., Bougerol, T., Bataille, B., Mattei, V., Dormont, D., Devaux, B., Vérin, M., Houeto, J.-L., Pollak, P., Benabid, A.-L., Agid, Y., Krack, P., Millet, B., Pelissolo, A., STOC Study Group, 2008. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N. Engl. J. Med. 359, 2121–2134. doi:10.1056/NEJMoa0708514

Martinowich, K., Lu, B., 2007. Interaction between BDNF and Serotonin: Role in Mood Disorders. Neuropsychopharmacology 33, 73–83.

May, A., 2011. Experience-dependent structural plasticity in the adult human brain. Trends Cogn. Sci. 15, 475–482. doi:10.1016/j.tics.2011.08.002

Micoulaud-Franchi, J.-A., Fond, G., Dumas, G., 2013a. Cyborg psychiatry to ensure agency and autonomy in mental disorders. A proposal for neuromodulation therapeutics. Front. Hum. Neurosci. 7, 463. doi:10.3389/fnhum.2013.00463

Micoulaud-Franchi, J.-A., Quiles, C., Vion-Dury, J., 2013b. Éléments pour une histoire de l'électricité et du cerveau en psychiatrie. Applications thérapeutiques de la stimulation externe et de l'enregistrement électrique en psychiatrie (Partie II). Ann. Méd.-Psychol. Rev. Psychiatr. 171, 323–328. doi:10.1016/j.amp.2013.03.007

Munafo, M.R., Thiselton, D.L., Clark, T.G., Flint, J., 2006. Association of the NRG1 gene and schizophrenia: a meta-analysis. Mol Psychiatry 11, 539–546.

Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527, 633–639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

Player, M.J., Taylor, J.L., Weickert, C.S., Alonzo, A., Sachdev, P., Martin, D., Mitchell, P.B., Loo, C.K., 2013. Neuroplasticity in depressed individuals compared with healthy controls. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 38, 2101–2108. doi:10.1038/npp.2013.126

Pope, H.G., Jr, Jonas, J.M., Hudson, J.I., Cohen, B.M., Gunderson, J.G., 1983. The validity of DSM-III borderline personality disorder. A phenomenologic, family history, treatment response, and long-term follow-up study. Arch. Gen. Psychiatry 40, 23–30.

Rosa, M.A., Lisanby, S.H., 2012. Somatic Treatments for Mood Disorders. Neuropsychopharmacology 37, 102–116. doi:10.1038/npp.2011.225

Rotarska-Jagiela, A., Oertel-Knoechel, V., DeMartino, F., van de Ven, V., Formisano, E., Roebroeck, A., Rami, A., Schoenmeyer, R., Haenschel, C., Hendler, T., Maurer, K., Vogeley, K., Linden, D.E.J., 2009. Anatomical brain connectivity and positive symptoms of schizophrenia: A diffusion tensor imaging study. Psychiatry Res. Neuroimaging 174, 9–16. doi:10.1016/j.pscychresns.2009.03.002

Saito, N., Kuginuki, T., Yagyu, T., Kinoshita, T., Koenig, T., Pascual-Marqui, R.D., Kochi, K., Wackermann, J., Lehmann, D., 1998. Global, regional, and local measures of complexity of multichannel electroencephalography in acute, neuroleptic-naive, first-break schizophrenics. Biol. Psychiatry 43, 794–802.

Shergill, S.S., Murray, R.M., McGuire, P.K., 1998. Auditory hallucinations: a review of psychological treatments. Schizophr. Res. 32, 137–150. doi:10.1016/S0920-9964(98)00052-8

Shin, L.M., Rauch, S.L., Pitman, R.K., 2006. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann. N. Y. Acad. Sci. 1071, 67–79. doi:10.1196/annals.1364.007

Skodol, A.E., Gunderson, J.G., Pfohl, B., Widiger, T.A., Livesley, W.J., Siever, L.J., 2002. The borderline diagnosis I: psychopathology, comorbidity, and personality structure. Biol. Psychiatry 51, 936–50.

Smith, K.S., Graybiel, A.M., 2014. Investigating Habits: Strategies, Technologies, and Models. Name Front. Behav. Neurosci. 8, 39.

Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T., Hjaltason, O., Birgisdottir, B., Jonsson, H., Gudnadottir, V.G., Gudmundsdottir, E., Bjornsson, A., Ingvarsson, B., Ingason, A., Sigfusson, S., Hardardottir, H., Harvey, R.P., Lai, D., Zhou, M., Brunner, D., Mutel, V., Gonzalo, A., Lemke, G., Sainz, J., Johannesson, G., Andresson, T., Gudbjartsson, D., Manolescu, A., Frigge, M.L., Gurney, M.E., Kong, A., Gulcher, J.R., Petursson, H., Stefansson, K., 2002. Neuregulin 1 and susceptibility to schizophrenia. Am. J. Hum. Genet. 71, 877–892. doi:10.1086/342734

Stephan, K.E., Baldeweg, T., Friston, K.J., 2006. Synaptic Plasticity and Dysconnection in Schizophrenia. Biol. Psychiatry 59, 929–939. doi:10.1016/j.biopsych.2005.10.005

Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Dysconnection in Schizophrenia: From Abnormal Synaptic Plasticity to Failures of Self-monitoring. Schizophr. Bull. 35, 509 –527. doi:10.1093/schbul/sbn176

Stern, A., 1938. Psychoanalytic Investigation of and Therapy in the Border Line Group of Neuroses. Psychoanal Q 7, 467–489.

Stevenson, J., Meares, R., Comerford, A., 2003. Diminished Impulsivity in Older Patients With Borderline Personality Disorder. Am J Psychiatry 160, 165–166. doi:10.1176/appi.ajp.160.1.165

Szekely, D., Polosan, M., 2010. Les thérapeutiques non médicamenteuses en psychiatrie. Ann. Méd.-Psychol. Rev. Psychiatr. 168, 546–551. doi:10.1016/j.amp.2010.06.020

Torgersen, S., Lygren, S., Øien, P.A., Skre, I., Onstad, S., Edvardsen, J., Tambs, K., Kringlen, E., 2000. A twin study of personality disorders. Compr. Psychiatry 41, 416–425. doi:10.1053/comp.2000.16560

Van der Kolk, B.A., Hostetler, A., Herron, N., Fisler, R.E., 1994. Trauma and the development of borderline personality disorder. Psychiatr. Clin. North Am. 17, 715–730.

Van Essen, D.C., 1997. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385, 313–318. doi:10.1038/385313a0

Vercammen, A., Knegtering, H., Liemburg, E.J., Boer, J.A. den, Aleman, A., 2010. Functional connectivity of the temporo-parietal region in schizophrenia: Effects of rTMS treatment of auditory hallucinations. J. Psychiatr. Res. 44, 725–731. doi:10.1016/j.jpsychires.2009.12.011

Vernay, M., Haesebaert, F., Poulet, E., 2012. Traitement par neuromodulation des hallucinations. Inf. Psychiatr. Volume 88, 831–838.

Wahlund, B., von Rosen, D., 2003. ECT of major depressed patients in relation to biological and clinical variables: a brief overview. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 28 Suppl 1, S21–26. doi:10.1038/sj.npp.1300135

Wernicke, C., 1906. Grundriss der Psychiatrie in klinischen Vorlesungen. Thieme, Leipzig, Germany.

White, T., Su, S., Schmidt, M., Kao, C.-Y., Sapiro, G., 2010. The development of gyrification in childhood and adolescence. Brain Cogn. 72, 36–45. doi:10.1016/j.bandc.2009.10.009

Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. The Lancet 382, 1575–1586. doi:10.1016/S0140-6736(13)61611-6

Wingenfeld, K., Spitzer, C., Rullkötter, N., Löwe, B., 2010. Borderline personality disorder: Hypothalamus pituitary adrenal axis and findings from neuroimaging studies. Psychoneuroendocrinology 35, 154–170. doi:10.1016/j.psyneuen.2009.09.014

Zanarini, M.C., Frankenburg, F.R., Reich, D.B., Silk, K.R., Hudson, J.I., McSweeney, L.B., 2007. The Subsyndromal Phenomenology of Borderline Personality Disorder: A 10-Year Follow-Up Study. Am J Psychiatry 164, 929–935. doi:10.1176/appi.ajp.164.6.929

Zannas, A.S., Binder, E.B., 2014. Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. Genes Brain Behav. 13, 25–37. doi:10.1111/gbb.12104

Zhang, L.I., Poo, M.M., 2001. Electrical activity and development of neural circuits. Nat. Neurosci. 4 Suppl, 1207–1214. doi:10.1038/nn753