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Investigation of neural activity in Schizophrenia during resting-state MEG: using non-linear dynamics and machine-learning to shed light on information disruption in the brain

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Investigation of neural activity in Schizophrenia during resting-state MEG: how non-linear dynamics and machine-learning can shed light on information disruption in the brain

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Résumé

Environ 25% de la population mondiale est atteinte de troubles psychiatriques qui sont typiquement associés à des problèmes comportementaux, fonctionnels et/ou cognitifs et dont les corrélats neurophysiologiques sont encore très mal compris. Non seulement ces dysfonctionnements réduisent la qualité de vie des individus touchés, mais ils peuvent aussi devenir un fardeau pour les proches et peser lourd dans l'économie d'une société. Cibler les mécanismes responsables du fonctionnement atypique du cerveau en identifiant des biomarqueurs plus robustes permettrait le développement de traitements plus efficaces. Ainsi, le premier objectif de cette thèse est de contribuer à une meilleure caractérisation des changements dynamiques cérébraux impliqués dans les troubles mentaux, plus précisément dans la schizophrénie et les troubles d'humeur. Pour ce faire, les premiers chapitres de cette thèse présentent, en intégral, deux revues de littératures systématiques que nous avons menées sur les altérations de connectivité cérébrale, au repos, chez les patients schizophrènes, dépressifs et bipolaires. Ces revues révèlent que, malgré des avancées scientifiques considérables dans l'étude de l'altération de la connectivité cérébrale fonctionnelle, la dimension temporelle des mécanismes cérébraux à l'origine de l'atteinte de l'intégration de l'information dans ces maladies, particulièrement de la schizophrénie, est encore mal comprise. Par conséquent, le deuxième objectif de cette thèse est de caractériser les changements cérébraux associés à la schizophrénie dans le domaine temporel. Nous présentons deux études dans lesquelles nous testons l'hypothèse que la « disconnectivité temporelle » serait un biomarqueur important en schizophrénie. Ces études explorent les déficits d'intégration temporelle en schizophrénie, en quantifiant les changements de la dynamique neuronale dite invariante d'échelle à partir des données magnétoencéphalographiques (MEG) enregistrés au repos chez des patients et des sujets contrôles. En particulier, nous utilisons (1) la LRTCs (long-range temporal correlation, ou corrélation temporelle à longue-distance) calculée à partir des oscillations neuronales et (2) des analyses multifractales pour caractériser des modifications de l'activité cérébrale arythmique. Par ailleurs, nous développons des modèles de classification (en apprentissage-machine supervisé) pour mieux cerner les attributs corticaux et sous-corticaux permettant une distinction robuste entre les patients et les sujets sains. Vu que ces études se basent sur des données MEG spontanées enregistrées au repos soit avec les yeux ouvert, ou les yeux fermées, nous nous sommes par la suite intéressés à la possibilité de trouver un marqueur qui

combinerait ces enregistrements. La troisième étude originale explore donc l'utilité des modulations de l'amplitude spectrale entre yeux ouverts et fermées comme prédicteur de schizophrénie. Les résultats de ces études démontrent des changements cérébraux importants chez les patients schizophrènes au niveau de la dynamique d'invariance d'échelle. Elles suggèrent une dégradation du traitement temporel de l'information chez les patients, qui pourrait être liée à leurs symptômes cognitifs et comportementaux. L'approche multimodale de cette thèse, combinant la magétoencéphalographie, analyses non-linéaires et apprentissage machine, permet de mieux caractériser l'organisation spatio-temporelle du signal cérébrale au repos chez les patients atteints de schizophrénie et chez des individus sains. Les résultats fournissent de nouvelles preuves supportant l'hypothèse d'une « disconnectivité temporelle » en schizophrénie, et étendent les recherches antérieures, en explorant la contribution des structures cérébrales profondes et en employant des mesures non-linéaires avancées encore sous-exploitées dans ce domaine. L'ensemble des résultats de cette thèse apporte une contribution significative à la quête de nouveaux biomarqueurs de la schizophrénie et démontre l'importance d'élucider les altérations des propriétés temporelles de l'activité cérébrales intrinsèque en psychiatrie. Les études présentées offrent également un cadre méthodologique pouvant être étendu à d'autres psychopathologie, telles que la dépression.

Mots clés : Schizophrénie, Dépression, État-de-repos, Magnétoencéphalographie, Apprentissage-machine, Criticalité, Invariance d'échelle, Psychiatrie, Connectivité, Multifractalité

Abstract

Psychiatric disorders affect nearly a quarter of the world's population. These typically bring about debilitating behavioural, functional and/or cognitive problems, for which the underlying neural mechanisms are poorly understood. These symptoms can significantly reduce the quality of life of affected individuals, impact those close to them, and bring on an economic burden on society. Hence, targeting the baseline neurophysiology associated with psychopathologies, by identifying more robust biomarkers, would improve the development of effective treatments. The first goal of this thesis is thus to contribute to a better characterization of neural dynamic alterations in mental health illnesses, specifically in schizophrenia and mood disorders. Accordingly, the first chapter of this thesis presents two systematic literature reviews, which investigate the resting-state changes in brain connectivity in schizophrenia, depression and bipolar disorder patients. Great strides have been made in neuroimaging research in identifying alterations in functional connectivity. However, these two reviews reveal a gap in the knowledge about the temporal basis of the neural mechanisms involved in the disruption of information integration in these pathologies, particularly in schizophrenia. Therefore, the second goal of this thesis is to characterize the baseline temporal neural alterations of schizophrenia. We present two studies for which we hypothesize that the resting temporal dysconnectivity could serve as a key biomarker in schizophrenia. These studies explore temporal integration deficits in schizophrenia by quantifying neural alterations of scale-free dynamics using resting-state magnetoencephalography (MEG) data. Specifically, we use (1) long-range temporal correlation (LRTC) analysis on oscillatory activity and (2) multifractal analysis on arrhythmic brain activity. In addition, we develop classification models (based on supervised machine-learning) to detect the cortical and sub-cortical features that allow for a robust division of patients and healthy controls. Given that these studies are based on MEG spontaneous brain activity, recorded at rest with either eyes-open or eyes-closed, we then explored the possibility of finding a distinctive feature that would combine both types of resting-state recordings. Thus, the third study investigates whether alterations in spectral amplitude between eyes-open and eyes-closed conditions can be used as a possible marker for schizophrenia. Overall, the three studies show changes in the scale-free dynamics of schizophrenia patients at rest that suggest a deterioration of the temporal processing of information in patients, which might relate to their cognitive and behavioural symptoms. The multimodal approach of this thesis, combining

MEG, non-linear analyses and machine-learning, improves the characterization of the resting spatiotemporal neural organization of schizophrenia patients and healthy controls. Our findings provide new evidence for the temporal dysconnectivity hypothesis in schizophrenia. The results extend on previous studies by characterizing scale-free properties of deep brain structures and applying advanced non-linear metrics that are underused in the field of psychiatry. The results of this thesis contribute significantly to the identification of novel biomarkers in schizophrenia and show the importance of clarifying the temporal properties of altered intrinsic neural dynamics. Moreover, the presented studies offer a methodological framework that can be extended to other psychopathologies, such as depression.

Keywords: Schizophrenia, Depression, Resting-state, Magnetoencephalography, Machine-Learning, Criticality, Scale-free, Psychiatry, Connectivity, Multifractality

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List of abbreviations

ACC: anterior cingulate cortex
ASRM: Altman self-rating mania scale
BD: bipolar disorder
BDI: Beck's depression inventory
C1: first log-cumulant
C2: second log-cumulant
CEN: central executive network
DA: decoding accuracy
DBS: deep brain stimulation
DFA: detrended fluctuation analysis
EEG: electroencephalography
EC: eyes-closed
EO: eyes-open
LRTC: Long-range-temporal-correlation
MDD: major depressive disorder
MEG : magnetoencephalography
MRI: magnetic resonance imaging
PFC: prefrontal cortex
RECO: relative difference in amplitude between eyes-closed and eyes-open conditions
RS: resting-state
SANS: Scale for the assessment of negative symptoms
SAPS: Scale for the assessment of positive symptoms
SVM: support vector machine
SZ: schizophrenia
WLBMF: Wavelet p-Leaders bootstrap Multifractal analysis

Dedication

This thesis is dedicated to my beloved uncle, Khosrow.

You moved oceans and united continents with your love, kindness and brilliant mind.

I promise to keep doing things that help people.

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Chapter 1 - Introduction

1.1 Background

Schizophrenia is a debilitating disorder with severe cognitive impairments. For over 20 years, it has been suggested that dysconnectivity within the brain, at both the anatomical and functional levels, underlines clinical symptoms of schizophrenia (Friston et al., 2016). The theory of dysconnectivity claims that patients symptoms are underlined by an overall failure of functional integration (Weinberger et al., 1992; Friston and Frith, 1995). This notion can even be seen within the origins of the term, *schizophrenia* (from the Greek, split mind), attributed to Eugen Bleuler in the 20th century (Kuhn, 2004), with the intention to move away from the misleading terminology of *dementia praecox* (i.e. early dementia).

The most influential classification system of the past decades has been the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013a). The DSM first popularized the Kraepelinian diagnostic approach (Kraepelin, 1921), which conceptualized psychotic and major mood disorders as two distinct and categorically exclusive disorders. This taxonomic system continues to affect the way patients are treated and how research is conducted (Weber and Engstrom, 1997; Craddock and Owen, 2005). The DSM defines Schizophrenia (SZ) as the diagnosis for a patient who presents with two or more of the following symptoms for one month, unless treated successfully: delusions, hallucinations, disorganized speech, disorganized/catatonic behavior, negative symptoms. Individuals must also present social and/or occupational dysfunction for a substantial amount of time, as well as continuous signs of disturbances for at least six months. Other diagnostic categories that have similar profiles (e.g., schizoaffective disorder and bipolar disorder) must be ruled-out (American Psychiatric Association, 2013a). Conversely, the DSM defines Major Depressive Disorder (MDD) as the diagnosis for a person who presents with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, significant weight gain/loss or appetite change, sleep disturbances, severe psychomotor change, tiredness/fatigue or low energy, sense of worthlessness or delusional guilt, impaired ability to think or make decisions, recurrent thoughts of death/suicidal ideation. Again, individuals must present with social and/or occupational dysfunction for a

substantial amount of time, and side-effects of drugs must be ruled out (American Psychiatric Association, 2013a).

The concept of dysconnectivity has been linked to the complex symptomology of SZ. Given this, the diagnostic criteria and subtyping of SZ and other psychopathologies have experienced many changes since the first edition of the DSM in 1952 (Pilecki et al., 2011). In particular, the poor validity, subjective and timing-based system of the DSM have been criticized by those in the field of psychiatry (Hyman, 2011; Nemeroff et al., 2013; Blashfield et al., 2014). Some clinicians and researchers have mentioned that it fails to take into account the heterogenous symptoms and co-morbidities present within patient groups (e.g. Hankin et al. 2005; Walton et al. 2011; Hengartner and Lehmann 2017). This has led to a lack of advancements and precision in the treatment for this disorder, as shown by the minimal level of innovation in psychotropics since the early 1990s (Miyamoto et al., 2012). Since then, pharmacological treatments have been slow to develop and are donned on patients through trial and error. The sluggish progress might be due to a lack of incentive, difficulty in translation of animal studies to human trials, brain complexity, and drug approval thresholds (O'Brien et al., 2014; van der Doef et al., 2018). This could also be due to the societal undervaluation of mental health compared to physical health (MacEwan et al., 2016), and oversight of the ramifications of mental health illnesses on the affected individual and their families.

Given the heterogeneity and complex prognosis of SZ, early diagnosis, prior to the accumulation of psychotic episodes and the confounding effects of medications, is the best way to equip at-risk individuals. Although the work of this thesis relies on DSM diagnoses, one way to improve on the current classification system is by opting for a dimensional or domain-based approach to patients' symptoms. Alternative strategies for the categorization of mental health disorders have been proposed, such as the Research Domain Criteria (RDoC) (Insel et al., 2010; Insel, 2014) and the Hierarchical Taxonomy of Psychopathology (HiToP)(Kotov et al., 2017), and will covered in the Discussion of this thesis in Chapter 6. Another way to improve on early detection of psychosis is to identify reliable and accessible biomarkers. Neuroimaging techniques have made great strides towards this effort and have helped untangle the neurophysiological underpinnings of psychopathologies (reviews: Van Den Heuvel and Fornito, 2014; Alamian et al., 2017b; Penadés

et al., 2019; Keshavan et al., 2020). However, given the lack of new drugs, personalized treatment options, specific biomarkers and the vague diagnostic criteria, it is clear that more work is needed to improve our understanding of the neurophysiology of schizophrenia. Novel approaches in characterizing the dysconnectivity that underlines patients' symptomatology might be the key to unlocking facets of this illness that have gone unnoticed until now.

1.2 Rationale

The overarching aim of this thesis is to use the alterations in the spatiotemporal structures of neural signal measured at rest, as a potential marker for psychopathologies. Abnormalities in local synchrony and long-range connectivity patterns seem to underline patients' symptomologies, and most studies have examined and characterized anatomical and functional changes in inter-regional brain connectivity using magnetic resonance imaging techniques (MRI) (reviews: Zhou et al., 2015; Giraldo-Chica and Woodward, 2016; Sheffield and Barch, 2016) but, fewer have investigated the changes in the temporal dynamics that take place in patients' intrinsic electrophysiological brain signals.

1.2.1 Resting-state

Studies in psychiatry that have examined alterations in the brain's electrophysiological signal have largely focused on event-related changes during cognitive tasks or emotional responses (e.g., task-based activity). What has been missing, is a clear and detailed characterization of what happens in terms of the intrinsic, temporal organization and neural functioning of psychiatric patients. In other words, what are their defining characteristics, over time, at rest, and how do they differ compared to healthy controls? This task-free baseline functioning can be tapped into with resting-state paradigms, during which participants lay still in a neuroimaging machine, with either their eyes closed (EC) or open (EO), and without executing any task. In such states, the neural signal measured is thought to speak of the fundamental organization – or disorganization – of the brain (Brookes et al., 2011; Buckner et al., 2008; Deco et al., 2011; Shehzad et al., 2009). While age is a factor known to alter resting-state networks' stability and organization in healthy brains (Song et al., 2012; Lacombe et al., 2015; Petti et al., 2016; Tsvetanov et al., 2016), these intrinsic

dynamics are also altered by psychiatric disorders and can reveal unique features of their pathophysiology (Broyd et al., 2009; Greicius, 2008; Fox and Greicius, 2010; Raichle et al., 2001). For instance, both neural structural and functional abnormalities have been found at rest among psychiatric patients, which correlate significantly with their symptomology (Dutta et al., 2014; Hanford et al., 2016; Northoff, 2016; Alamian et al., 2017b, 2017a). However, several questions about the neurophysiological bases of these alterations, particularly in terms of arrhythmic brain activity, still remains unanswered

Electrophysiological studies, and especially magnetoencephalography (MEG) studies, use EC and EO resting-state paradigms interchangeably but, the differences that can emerge between these conditions, and their potential relationship with disease, are still unclear. Some studies suggest that the relative difference between EO and EC could be a potential marker for pathology (Nikulin and Brismar, 2004; Bosboom et al., 2006; Ikeda et al., 2020). This is of particular interest in the schizophrenia population, where neural dysconnectivity is present independently of any specific task (Ma et al., 2012; Orban et al., 2018).

1.2.2 Rhythmic vs arrhythmic

Electrophysiological brain activity can be categorized as either rhythmic or arrhythmic. Rhythmic brain activity (also known as oscillations) arises from the synchronization of small neural populations and expands across multiple temporal and spatial scales. It involves the local integration of information within brain areas specializing in the same functions and long-range connections that join different modalities (Varela et al., 2001). Rhythmic brain activity can be assessed by characterizing the spatiotemporal features of neural oscillations. Spectral power analyses capture local brain activity by informing on the magnitude of synchronization in each frequency band (Ward, 2003). This type of analysis can be carried out using the Fast Fourier Transform (FFT) for frequency domain decomposition, and the Wavelet and the Hilbert-Huang transforms for time-frequency decompositions (Tallon-Baudry and Bertrand, 1999; Puliafito et al., 2017; Abry et al., 2019). On the other hand, coupling estimations of time-series have been used to tap into long-range synchronizations (or connectivity). This can be done through a number of

metrics, such as imaginary coherence (Nolte et al., 2004) and weighted phase lag index (Vinck et al. 2011).

Although non-rhythmic (or arrhythmic) brain activity accounts for an important part of the electric brain signal (Bullock et al., 2003; He et al., 2010), very little is known about it. While at first considered only as background noise, which was typically removed from the signal, arrhythmic the community has come to appreciate that the brain activity in fact contains arrhythmic structure that can be characterized using non-linear signal processing (He et al., 2010; He, 2014). This type of neural activity is easily recognizable as its temporal power spectrum typically follows a straight negative slope, which can be described as $1/f^{\beta}$ power-law, when viewed in a log/log plot. As can be seen in Figure 1, local rhythmic activities (oscillations), which are often the focus of neuroimaging studies, appear as peaks in this $1/f^{\beta}$ distribution. The presence of arrhythmic brain activity has been reported across the neuroimaging literature, and is thought to arise from non-linear dynamical processes (e.g., Tononi et al. 1994; Friston 1996, 1998; Takahashi 2013). Interestingly, these dynamics are characteristic of systems in a state of dynamical criticality (Beggs and Plenz, 2003; Stam and De Bruin, 2004; Kitzbichler et al., 2009; Fraiman and Chialvo, 2012; Blythe and Nikulin, 2017; Palva and Palva, 2018).

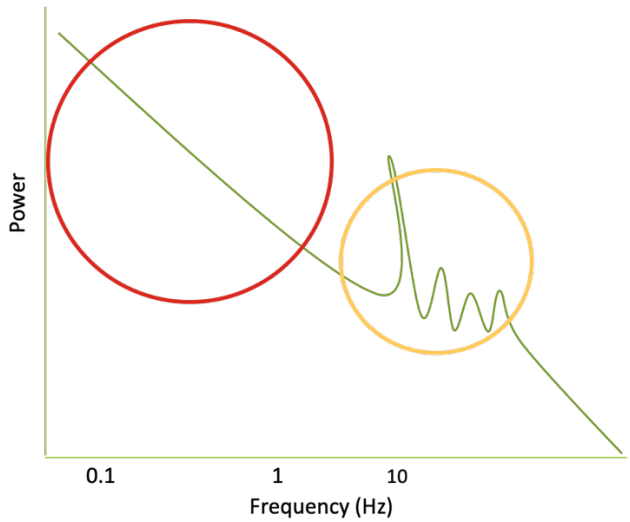


FIGURE 1: SKETCH OF A LOG-LOG POWER SPECTRUM PLOT

Sketch illustrating the arrhythmic and rhythmic (oscillations, bumps) parts of brain activity, by plotting the logarithmic transformation of frequency against power. It also highlights the prominent presence of 1/f, scale-invariant, activity throughout the signal.

When the brain is in a state of criticality, it is thought to be at a transitional phase, between order and disorder (Beggs and Timme, 2012; Cocchi et al., 2017; Souza França et al., 2018). The brain requires this balance between regularity (structure) to maintain consistent behaviour, and flexibility (local variability) to adapt to incoming information and environmental changes (R. Chialvo, 2004; Beggs and Timme, 2012). Critical dynamics have been found to be necessary for optimal information integration and maximal propagation in the brain (Socolar and Kauffman, 2003; Haldeman and Beggs, 2005; Fraiman and Chialvo, 2012). This state is also important for producing proper and efficient responses to internal or external stimuli (Beggs and Plenz, 2003; Shew et al., 2011; Beggs and Timme, 2012; Haimovici et al., 2013; Samek et al., 2016), and is thought to affect the functioning of oscillations and local synchronizations (Palva and Palva, 2018).

The emerging neural signal from the state of criticality is said to be scale-free, such that its properties are preserved across spatiotemporal scales (like in Figure 1). More specifically, the dynamical features of criticality show fractal geometry (i.e., patterns within the signal look the same regardless of magnification scales and statistically equivalent), 1/f power-law correlations, and fast transitions in (inhibitory or excitatory) metastates (Plenz and Chialvo, 2009; Cocchi et al., 2017; Chialvo, 2018; Palva and Palva, 2018). Scale-free dynamics can be found in both rhythmic and arrhythmic neural activity (Lin et al., 2016), and are best captured through the combined measures of self-similarity and multifractality (more in Chapter 4). Disease and psychopathologies can affect the physical and temporal structures of resting brain signals (e.g., Beggs and Timme, 2012; Nikulin et al., 2012; Takahashi, 2013).

Different analytical approaches have been proposed to evaluate the properties of arrhythmic brain activity. For this thesis, I focused on the Wavelet p-Leader and Bootstrap based MultiFractal (WLBMF) analysis (Wendt and Abry, 2007; Wendt et al., 2007) to evaluate the features of self-similarity and multifractality on the low-frequency arrhythmic part of the brain signal. Additionally, Detrended Fluctuation Analysis (DFA) was used to measure long-range-temporal-correlations (LRTCs) in the amplitude dynamics of oscillatory bands (Linkenkaer-Hansen et al.,

2001b; Hardstone et al., 2012; Nikulin et al., 2012). The presence of LRTCs are thought to reflect the integrity and memory of information, which slowly decays over time, following a 1/f power-law distribution (Linkenkaer-Hansen et al., 2001b).

1.2.2.1 Application of scale-free dynamics in psychiatry

Together, these metrics can inform on the changes in scaling properties and criticality in rhythmic and arrhythmic brain activity in psychiatric patients compared to healthy controls (Beggs and Timme, 2012; Nikulin et al., 2012; Takahashi, 2013; Zimmern, 2020). In the schizophrenia literature, a number of studies have reported altered scale-free dynamics based on fractal analysis of the 1/f EEG rhythm (Slezin et al., 2007a), LRTCs of EEG oscillation amplitudes (Nikulin et al., 2012; Junfeng Sun et al., 2014; Moran et al., 2019) and power-law distributions on fMRI data (Radulescu et al., 2012). These studies show that schizophrenia patients show smaller power-law exponents and less autocorrelation over time in the anterior prefrontal cortex, which are indicative of a shift towards white noise (randomness). These changes in scale invariant properties may be linked to reduced responsiveness in patients (Zimmern, 2020). In the depression literature, opposing findings about the LRTCs of broadband EEG oscillations have been observed, with one study reporting larger (Lee et al., 2007) and another smaller (Wang et al., 2016a) DFA exponents compared to controls. A review of EEG complexity findings in depression reported that fractal dimension (*D*) and entropy metrics were typically larger in patients than controls in frontal and parietal brain regions, during both resting-states and emotional-induction tasks (Akdemir Akar et al., 2015). Given the prominence of $1/f^{\beta}$ distribution in brain activity, it is possible that it is in fact this activity that dictates the structure of brain patterns and underline temporal disruptions in information processing in psychiatric patients. Thus, it is clear that an understanding of scale-free neural dynamics is needed to fully grasp how the brain operates in health and disease (Zimmern, 2020).

1.2.3 Using MEG to study the fundamental organization of the brain

Given that the scope of this thesis was to investigate intrinsic neural changes in temporal dynamics in psychiatric populations, it was important to select a neuroimaging technique with high temporal

resolutions. MEG has emerged as a valuable, non-invasive, functional imaging tool for clinical and translational research in psychiatry (Cohen, 1972; Siekmeier and Stufflebeam, 2010; Williams and Sachdev, 2010). Its sub-millisecond temporal resolution allows to confidently examine alterations of scale-free dynamics in the temporal domain. Moreover, MEG extends beyond previously used EEG-based methods and reliably estimates data from cortical and, possibly, sub-cortical regions. The main generators of MEG signals are thought to be the agglomeration of postsynaptic potentials, resulting from the synchrony of microcolumns of tens of thousands of pyramidal neurons (Hamalainen et al., 1993; Nunez and Silberstein, 2000; Baillet, 2017). The electric currents associated with the PSPs produced among dendrites are believed to be at the source of most detectable MEG/EEG signals, as they last longer than action potentials (Nunez, 1981). Figure 2 below, borrowed with permission from Baillet (2017), illustrates the sources of MEG signals.

The recording of the electrical signals is fairly straight forward in contrast to the magnetic brain signals, which require more complex recording and analytical techniques due to their low field strength (Stam, 2010). These include cooling of conductive coils using helium, the use of superconducting quantum interference devices (SQUIDs) and gradiometers to improve signal-to-noise ratio. In addition, while EEG and MEG are closely related, the magnetic field is less sensitive to signal distortions caused by head tissues than the electrical potential. While MEG's spatial resolution cannot match that of f(MRI), available co-registration techniques allow for cm-level spatial localization of neural activity (e.g., Gramfort et al., 2013). Of note, recent MEG studies have reported successful source estimation in deep structures (Krishnaswamy et al., 2017; Recasens et al., 2018; Andersen et al., 2020), and have opened a novel path for the identification and characterization of scale-free changes in the neural signal of cortical and subcortical brain regions. The advantages of MEG and its' application on clinical research are further discussed in Chapter 2.

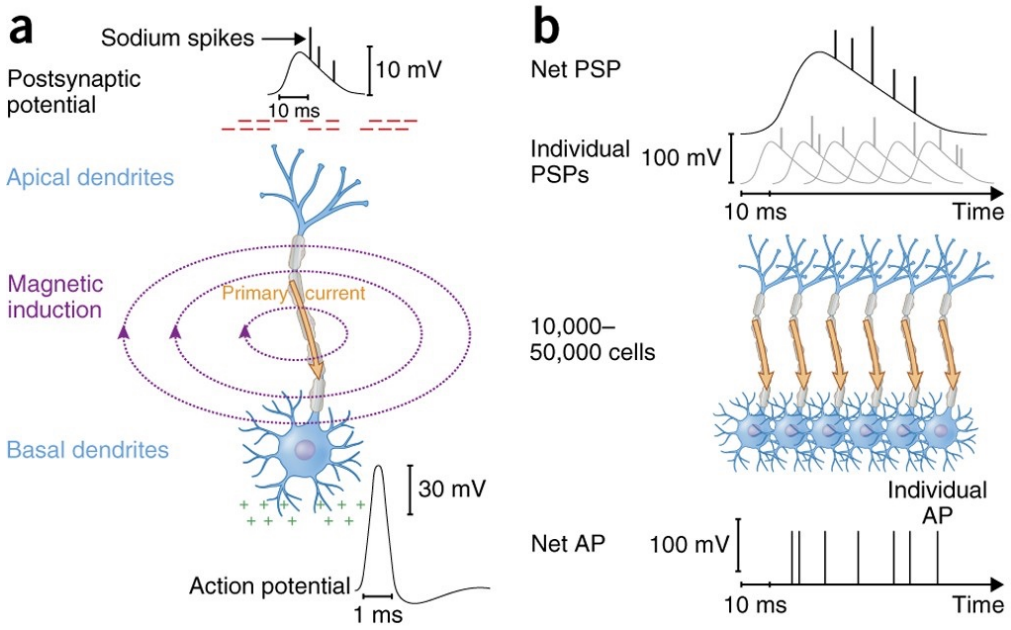


FIGURE 2: ILLUSTRATION OF MEG SIGNAL GENERATORS

Figure from Baillet, 2017, reproduced with permission from the author. *(a) For simplicity, we take the cortical pyramidal neuron to epitomize the elementary cellular generator of MEG signals. All physiological currents from all cell types generate a magnetic induction; the elongated morphology of the pyramidal neuron constrains the net primary current circulation along the cell, which is a factor in creating greater signal strength in comparison to those from more stellate cellular morphologies. The primary current results from an imbalance in electrical potentials between the apical dendritic arborescence of the cell and its soma and more basal dendrites. The magnetic induction isolines in purple are perpendicular to the primary current flow and can be picked up outside the head. The sources are twofold: the postsynaptic potentials (PSPs), including fast, large-amplitude sodium spikes, and axonal discharges (action potentials, AP). The slower components of the PSPs are substantially smaller in amplitude than the APs. (b) At the scale of cell assemblies, the mass effect of slower PSPs is stronger than that of APs owing to their greater overlap in time without requiring rigorous synchronization. Computational models and empirical evidence show that a minimum of 10,000 to 50,000 cells are required to produce a signal detectable with MEG. It is possible, in principle, that fast PSP spiking activity, and possibly shadows of APs, are detectable in MEG.*

1.2.4 Machine-learning

Over the past decade, supervised machine-learning has emerged as an important extension to conventional statistical methods to help classify groups of individuals (e.g. patients and healthy controls) based on a single metric or combination of variables. Its application in neuroscience and psychiatry-related data (Mumtaz et al., 2015; Zheng et al., 2015; Huys et al., 2016) is on the rise given that it is a practical way to data-mine neuroimaging, genetic, neurocognitive, and

behavioural features, to improve patient classification and the ability to predict prognosis, among other things (Librenza-Garcia et al., 2017).

Conventional statistics (i.e., T-tests, ANOVA, etc.) and machine-learning are complementary, but conceptually different, analytical techniques; the former allows for population-level inferences, while the latter allows for generalizable predictions (Bzdok et al., 2018). Specifically, classical statistics require the choice of a model based on *apriori* knowledge about the system, while statistical learning requires the choice of a predictive algorithm based on its capabilities in classifying groups in similar past scenarios (data-driven). Furthermore, while the function of conventional statistics is to reject the null-hypothesis and provide estimates for the sample itself (Wasserstein and Lazar, 2016), the core function of machine-learning is to produce accuracy predictions in "new" datasets. Indeed, the added bonus of cross-validation in machine-learning is its estimate of the generalizability of a classification pattern based on one dataset, extrapolated onto a new (out-of-sample) dataset.

Figure 3 summarizes the global steps involved in supervised machine-learning. This approach consists of 'training' a statistical model using an already labeled dataset in order to find a classification function that can separate two or more classes. Briefly, the procedure begins with transforming continuous MEG data into matrices of features (N*M; N:number of samples/subjects M: the number of computed features) that can later be used by a statistical learning model. Here, feature extraction is used to compute attributes of interest (e.g., power, scale-free metrics, genetic information).The model is then trained on a sub-portion of the data, called a *training-set,* using their correct labels (e.g., patient or control in a 2-class analysis), and assessed on the other portion of the dataset, called *test-set*. Next, the performance of the classifier is computed using a decoding accuracy (DA), which calculates the percentage of examples that were correctly classified overall (e.g., how many patients were correctly classified as being patients across the total number of subjects). In order to prevent the model from overfitting to the *training-set* and thus fail to generalize onto new samples, this process is repeated iteratively with different random splits, until all samples have been used as *test-sets* (i.e. cross-validation). The averaged DA is then used as the performance metric of the classification of the two groups. Lastly, given that clinical studies are

typically constrained to small sample sizes, statistical tests are needed to assess the significance of the obtained DA (e.g., we the use of permutations tests (Combrisson and Jerbi, 2015)).

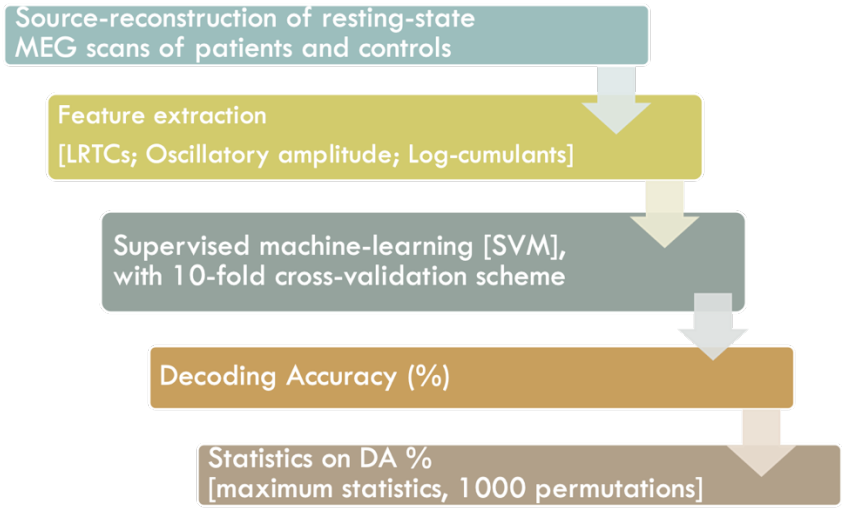


FIGURE 3: ILLUSTRATION OF MACHINE-LEARNING PIPELINE USING MEG DATA
Summary of the machine-learning framework for MEG data analysis. DA = decoding accuracy, LRTCs = long-range temporal correlations, MEG = magnetoencephalography.

In the field of psychiatry, machine-learning can help clinically-relevant information surface from the complex profile of patients (Iniesta et al., 2016; Bzdok and Meyer-Linderberg, 2018; Dwyer et al., 2018). This is particularly useful when dealing with the challenge of large datasets ("Big Data", e.g., multisite EEG data or combinations of behavioural, genetic and cognitive data), which involve heterogenous and uneven measurements across participants (e.g., missing data). The decoded pattern could reveal critical mechanistic properties of an illness that would have gone otherwise ignored if the analysis was to be solely based on *apriori* knowledge. A number of studies have applied machine-learning algorithms to brain data in the context of schizophrenia research (Veronese et al., 2013; Orban et al., 2018; De Filippis et al., 2019; Schnack, 2019; Tai et al., 2019), and have highlighted the potential benefits for precision medicine, for progress in the search of biomarkers and for the general improvement of our understanding of this illness. However, to date, few studies have used a machine-learning approach to study the resting- neuromagnetic signal of psychiatric patients. Specifically, one study used Support Vector Machine (SVM) to classify SZ patients and controls (Zhang et al., 2015), one used Bayesian Linear Regression to predict

depression based on resting-state power and a new study used resting-state MEG features to differentiate MDD and Bipolar Disorder (BD) patients.

1.3 Aim and hypotheses

The overarching aim of this thesis was to examine and measure the intrinsic neural dynamics of psychiatric disorders, with a focus on schizophrenia. Specifically, the first goal of this thesis was to understand how local and long-range synchrony are altered in rhythmic brain activity in schizophrenia and mood disorder patients during resting-state (Chapter 2). Moreover, given that the main focus of previous research studies has been on the spatial and functional changes in oscillatory synchrony, the second goal of this thesis was to characterize temporal alterations of resting-state MEG signal in schizophrenia in both rhythmic and arrhythmic activity using non-linear analyses (Chapters 3 and 4). Based on the current theory of dysconnectivity, we hypothesized that the temporal and structural organization of the resting neural signal of schizophrenia patients would be different from those of healthy controls. Specifically, we predicted reduced autocorrelation, more variability (Chapter 3), and less complexity in the neural signal of patients compared to controls (Chapter 4), within frontotemporal brain areas. We also predicted that machine-learning algorithms would successfully differentiate patients and controls using scale-free metrics, with a strong decoding accuracy. Lastly, given that resting-state paradigms (EO and EC) are currently used interchangeably in electrophysiological studies, and that differences in the two conditions has been shown to correlate with information receptivity, the third goal of this thesis was to examine whether EC, EO (or the ratio of the two) resting-sate MEG paradigms could reveal differential alterations in schizophrenia patients (Chapter 5). We hypothesized that new alterations in reactivity, as measured by differences in amplitude between EC and EO resting-state conditions, would emerge in schizophrenia.

1.3.1 Structure of the thesis

In the next chapter of this thesis, I present two literature reviews: (1) a systematic review on alterations in resting-state connectivity patterns in schizophrenia titled *Measuring alterations in oscillatory brain networks in schizophrenia with resting-state MEG: State-of-the-art and*

methodological challenges, published in Clinical Neurophysiology (2017), and (2) a critical review on alterations in resting-state connectivity in mood disorders, titled *Alterations of intrinsic brain connectivity patterns in depression and bipolar disorders: A critical assessment of magnetoencephalography-based evidence*, published in Frontiers in Psychiatry (2017). These reviews also highlight the utility and challenges of the application of MEG in clinical research. The third chapter of this thesis presents an original study titled *Patient, interrupted: MEG oscillation dynamics reveal temporal dysconnectivity in schizophrenia*, published in NeuroImage: Clinical (2020). In this article, I present our findings on how long-range-temporal-correlations (LRTCs) are altered in chronic schizophrenia patients at the cortical and subcortical levels and show how this metric could be a strong marker for schizophrenia. In the fourth chapter of this thesis, I present a study titled *Altered brain criticality in Schizophrenia: New insights from MEG*, under review in Frontiers in Neural Circuit. In this article, I present our findings on how measures of criticality (i.e. self-similarity and multifractality) are altered in chronic schizophrenia patients at the cortical level, and their significant correlations with patient's symptoms severity scores and medication dosage. The fifth chapter presents our findings about the predictive power of resting-state paradigms in classifying schizophrenia patients and controls. Spectral amplitudes in EO, EC, and the relative amplitude differences in EO and EC, were used as features in a supervised classification algorithm to determine which resting-state paradigm would reveal the most predictive markers of schizophrenia. The related article work entitled, *Unraveling spectral changes with resting-state MEG in Schizophrenia: eyes open, closed or both ?,* is in preparation and will be soon submitted to bioRxiv. In the final chapter of this thesis, I discuss our overall results in schizophrenia, the contributions of our studies to the field of psychiatry, their limitations and future applications to new clinical cohorts of depressive patients.

Chapter 2: Reviews of the literature

2.1 Measuring alterations in oscillatory brain networks in Schizophrenia with resting-state MEG: State-of-the-art and methodological challenges

Abstract

Neuroimaging studies provide evidence of disturbed resting-state brain networks in Schizophrenia (SZ). However, untangling the neuronal mechanisms that subserve these baseline alterations requires measurement of their electrophysiological underpinnings. This systematic review specifically investigates the contributions of resting-state Magnetoencephalography (MEG) in elucidating abnormal neural organization in SZ patients. A systematic literature review of resting-state MEG studies in SZ was conducted. This literature is discussed in relation to findings from resting-state fMRI and EEG, as well as to task-based MEG research in SZ population. Importantly, methodological limitations are considered and recommendations to overcome current limitations are proposed. Resting-state MEG literature in SZ points towards altered local and long-range oscillatory network dynamics in various frequency bands. Critical methodological challenges with respect to experiment design, and data collection and analysis need to be taken into consideration. Spontaneous MEG data show that local and global neural organization is altered in SZ patients. MEG is a highly promising tool to fill in knowledge gaps about the neurophysiology of SZ. However, to reach its fullest potential, basic methodological challenges need to be overcome. MEG-based resting-state power and connectivity findings could be great assets to clinical and translational research in psychiatry, and SZ in particular.

2.1.1 Introduction

Schizophrenia (SZ) is a severe psychotic disorder with important cognitive impairments. It is one of the most debilitating psychiatric illnesses. Worldwide, an estimated 21 million individuals suffer from schizophrenia and other psychotic illnesses (World Health Organization, 2016). SZ

patients display psychotic symptoms (e.g., hallucination, delusion, etc.) and often mood symptoms such as depression (American Psychiatric Association, 2013). Despite a thriving body of research, progress in understanding the pathophysiological mechanisms that underlie the symptoms of the disorder, and its heterogeneous nature, is relatively slow. Indeed, since its neural underpinnings are still up for debate (Tandon et al., 2013), the diagnosis of SZ mainly relies on clinical examination. Moreover, given that SZ patients often demonstrate treatment resistance (Elkis, 2007), a better understanding of this pathology could also help define new targets for treatment.

Important achievements over the years have come in part through advances in brain imaging techniques and methodological frameworks to study brain signal analyses. Over the last fifteen years, the exploration of brain function has moved away from solely studying local mechanisms, and towards adopting a large-scale network perspective, where both local activity and inter-regional interactions are examined (Varela et al., 2001; Alamian et al., 2017a). The recognition that the brain is more than the sum of its parts has naturally found its way into clinical research (Linden, 2012). For instance, functional alterations in intrinsic brain network organization observed with functional magnetic resonance imaging (fMRI) are thought to speak of the nature of the illness (Fox and Raichle, 2007; Greicius, 2008; Broyd et al., 2009; Fox and Greicius, 2010; Woodward and Cascio, 2015). In psychiatric patients, alterations in resting-state connectivity patterns have been shown to correlate with clinical symptoms (e.g., psychosis, depression). In SZ, aberrant brain network patterns have been observed using fMRI data that were acquired both during the performance of cognitive tasks, as well as during resting-state paradigms (Abel and Nickl-Jockschat, 2016). More globally, a steady flow of studies, showing altered functional connectivity patterns in SZ patients compared to matched healthy controls, have fueled the notion that impaired long-range neuronal communication plays a critical role in this clinical population.

Interestingly, alterations in connectivity observed through neuroimaging modalities have provided support to theoretical models that link certain neurophysiological circuits to pathological symptoms, such as the *disconnection syndrome* (Friston and Frith, 1995; Friston, 1996; Stephan et al., 2009) and *cognitive dysmetria* (Andreasen et al., 1998, 1999). Indeed, disconnectivity as a core dysfunction in SZ was proposed 20 years ago as a theoretical link between recent knowledge involving brain networks in cognition and former psychopathological theories of SZ. This theory

relies on the assumption that disorganization is a key node in SZ (Friston et al., 2016). Indeed, SZ is marked by patterns of symptoms involving errors in predictive coding (leading to delusion and hallucinations), lack of language and thought organization, and even, in some cases, motor disorganization. The disconnectivity hypothesis is thought to arise from aberrant synaptic plasticity, which has been attributed to abnormal modulation of N-methyl-D-aspartate (NMDA) receptors by neurotransmitters such as serotonin, dopamine and acetylcholine (Stephan et al., 2009). It has been proposed that these abnormal neural connections, occurring in distinct brain regions (cortical, subcortical, including the cerebellum, Yeganeh-Doost et al. 2011), thereby lead to clusters of symptoms in different domains (e.g., cognitive, affective and motor). This gives support to the *cognitive dysmetria* hypothesis (Andreasen et al., 1998, 1999).

Taken together, given the theoretical importance attributed to connectivity in the field of SZ, further investigations are needed to characterize the underlying altered mechanisms from a network perspective. Models such as the *cognitive dysmetria* and the *disconnection syndrome* can be probed, confirmed and extended using electrophysiological measures of neural network dynamics (Smart et al., 2015).

Indeed, while fMRI and MRI-based techniques such as diffusion tensor imaging (DTI) provide important functional and structural information to our understanding of pathological neural function, there is much to gain from techniques that provide direct access to neurophysiological brain signals. This is particularly true when aiming to assess alterations of neural synchronization patterns (i.e. local and long-range rhythmic fluctuations of brain activity) that operate at time scales that cannot be captured with fMRI. Consequently, electroencephalography (EEG) and magnetoencephalography (MEG), which have millisecond-range temporal resolution have been increasingly used to capture the missing pieces of information about how local and long-range oscillatory patterns change across brain regions in healthy and pathological populations (Brookes et al., 2011b). Fine-grained temporal resolution is critical as synchronized neuronal populations give rise to fast rhythmic fluctuations of activity with periodicities in multiple frequency bands, ranging in some cases from frequencies below 1 Hz up to well above 100 Hz.

Synchronization of neural populations is thought to reach far across numerous temporal and spatial scales, from local integration to long-range communication between distant neuronal assemblies (Varela et al., 2001). Generally speaking, in EEG and MEG, *local synchrony* is thought to be captured by the power estimation of data from one channel or cortical source. In contrast, *long-distance synchrony* is captured by estimating the connectivity between two brain signals. Functional connectivity is useful to describe the statistical dependency of time-series' activity arising from two brain areas (Schoffelen and Gross, 2009; Friston, 2011; Hillebrand et al., 2012), which may or may not be anatomically linked. It can be measured using linear and non-linear tools such as correlations, coherence, phase-lag index and mutual information (Stam et al., 2007; Knösche and Tittgemeyer, 2011; Sakkalis, 2011; Wang et al., 2014). Throughout this review, measures of distant neuronal interactions are described using the terms *connectivity*, *coupling* and *long-range synchrony/synchronization*, interchangeably.

It is now well-established that alterations in local and long-range oscillatory behavior could disrupt communication and lead to aberrant information processing and pathological symptoms in SZ (Rotarska-Jagiela et al., 2010; Pettersson-Yeo et al., 2011; Yu et al., 2012, 2013; Karbasforoushan and Woodward, 2012; Uhlhaas and Singer, 2013; Uhlhaas, 2013; Alderson-Day et al., 2015; Narr and Leaver, 2015; Ramani, 2015; Ćurčić-Blake et al., 2016; Giraldo-Chica and Woodward, 2016; Northoff and Duncan, 2016). Thus, in order to elucidate the neuronal underpinnings of SZ from a neural circuit perspective, the ability to examine local and long-range synchronization is critical. As explained above, such oscillatory brain mechanisms are best captured using electrophysiological measurement techniques such as MEG or EEG. Furthermore, a better understanding of the electrophysiological properties of spontaneous large-scale brain dynamics in SZ will also benefit and complement neuromodulation studies, such as transcranial direct-current stimulation (TDCS) or transcranial magnetic stimulation (TMS) (Neuling et al., 2015), which have been used as potential treatment for hallucinations (Brunelin et al., 2012; Mondino et al., 2016).

While for many reasons, including accessibility and clinical routine, numerous EEG studies have been conducted in SZ patients, the use of MEG to elucidate the intrinsic network anomalies associated with the illness is still in its early days. In addition, while the importance of examining

the intrinsic organization of brain networks within multiple frequency bands has gained scientific recognition, it is still a blooming tool in the field of psychiatry (e.g. Schmidt et al., 2014).

Hence, the goal of this review is to present an up-to-date survey of MEG resting-state spectral power and connectivity literature in the SZ population, and discuss it in relation to findings from fMRI and EEG, as well as to task-based MEG findings in the same population. Most importantly, we discuss methodological considerations and provide recommendations to overcome current limitations.

To date, two reviews dedicated to MEG resting-state findings in SZ can be found (Hinkley et al., 2010; Siekmeier and Stufflebeam, 2010). These have largely focused on power alterations. More recently, a paper summarizing the most prominent EEG and MEG findings of connectivity (and a few power) changes in SZ has been published (Maran et al., 2016). Finally, the benefits and challenges of MEG-based exploration in SZ have also been discussed as part of a wider review on the utility of MEG in psychiatric research (Uhlhaas et al., 2017). The scope and focus of the present review is different from the previously mentioned papers. Here, we provide – to the best of our knowledge – the most exhaustive and up-to-date account of all MEG evidence of inter-areal connectivity and power alterations in resting-state brain data in SZ. Additionally, by comparing MEG resting-state findings to those of fMRI and EEG, we draw a multimodal picture of the neurophysiological network-level mechanisms underlying SZ. Finally, our discussion of methodological pitfalls and practical recommendations provides a critical but constructive account of the field, hence, highlighting its future potential.

This paper is organized as follows. Sections 2.1.2 and 2.1.3, provide a brief overview of altered resting-state neural connectivity patterns in SZ that have been reported with fMRI and EEG resting-state studies, respectively. Section 2.1.4 provides a systematic account of resting-state MEG findings in schizophrenia population published to date, including alterations in local oscillatory power (subsection 2.1.4.1) and changes in long-range inter-areal coupling (subsection 2.1.4.2). The strengths and limitations of the reviewed resting-state MEG studies are then discussed in subsection 2.1.4.3, which is followed by a discussion on the link between task-based and task-free findings in SZ with MEG (subsection 2.1.4.4). Section 2.1.5 presents a critical

account of methodological considerations, pitfalls and recommendations for future research. Finally, sections 2.1.6 and 2.1.7 provide a general discussion and concluding remarks.

2.1.2 Resting-state fMRI findings in SZ patients: A brief overview

Given that the primary focus of the current review is centered on pathological changes of spontaneous (i.e. task-free) brain activity in SZ measured by MEG, we will first overview evidence on altered intrinsic neural communication in this population coming from resting-state studies with fMRI (this section) and EEG (Section 2.1.3).

There is a growing literature of fMRI-based connectivity studies, as well as extensive reviews, which report abnormal resting-state (RS) connectivity in SZ population (Rotarska-Jagiela et al., 2010; Pettersson-Yeo et al., 2011; Karbasforoushan and Woodward, 2012; Uhlhaas, 2013; Yu et al., 2013; Alderson-Day et al., 2015; Narr and Leaver, 2015; Ramani, 2015; Ćurčić-Blake et al., 2016; Northoff and Duncan, 2016). These reports largely converge by concluding that alterations in functional connectivity are observed across numerous key brain regions in SZ, even in the absence of a task.

Of note, enhanced connectivity between the thalamus and sensory and motor areas has been reported and replicated numerous times in SZ (Karbasforoushan and Woodward, 2012; Woodward et al., 2012; Klingner et al., 2014; Cheng et al., 2015; Wang et al., 2015a; Giraldo-Chica and Woodward, 2016). A recent study by Cheng et al (2015) analyzed the network connectivity of a large cohort of patients and controls ($n > 400$ for each group) and observed hyperconnectivity over the somato-motor areas in SZ (Cheng et al., 2015). Furthermore, compared to controls, patients show an enhanced RS long-range synchronization between temporal/parietal and sensory brain regions (Jafri et al., 2008; Karbasforoushan and Woodward, 2012; Woodward et al., 2012; Tu et al., 2013), as well as between PFC and posterior middle temporal cortex (Friston and Frith, 1995; Friston, 1996). Moreover, SZ patients appear to display increased connectivity between DMN and PFC regions (Whitfield-Gabrieli et al., 2009; Ongür et al., 2010). Some researchers have suggested that hyperconnectivity within RS networks is indicative of increased distraction due to psychotic experiences (Jafri et al., 2008; Broyd et al., 2009). Hypoconnectivity is also observed in SZ

patients, particularly within the PFC, and between subcortical regions (e.g., thalamus, caudate) and the PFC (Karbasforoushan and Woodward, 2012; Woodward et al., 2012; Tu et al., 2013; Cheng et al., 2015; Giraldo-Chica and Woodward, 2016). Decreased RS connectivity has been found between DMN and CEN in individuals with SZ or at high risk of developing SZ (Zhou et al., 2007; Whitfield-Gabrieli et al., 2009). Some researchers have suggested that this hypoconnectivity, specifically disrupted effective connectivity, could be a trademark of the SZ pathology (Friston and Frith, 1995; Friston, 1996, 1998; Weinberger et al., 1996; Riehemann et al., 2001)

In addition, connections relating to the thalamus are recurrently discussed with respect to the DMN and the CEN in SZ patients (Zaytseva et al., 2015). Specifically, there have been reports of decreased long-range connectivity between subcortical regions (e.g. amygdala) and frontal brain regions that are either part of the DMN, CEN or saliency network, such as the dorsolateral PFC, medial PFC and ACC (Welsh et al., 2010; Woodward et al., 2012; Liu et al., 2014; Cheng et al., 2015; Wang et al., 2015a; Sheffield and Barch, 2016).

Finally, several studies indicate that the saliency network, particularly one of its components, the anterior insula, is critically involved in the sense of interoception (e.g. Craig 2009). The SZ literature reports decreased connectivity between saliency network components (dorsal ACC, anterior insula) and CEN (dorsolateral PFC), and between saliency network (insula) and visual cortices (Northoff and Duncan, 2016). Alterations in this area could be linked to patients' difficulties in making sense of certain internal functions that are mistakenly attributed to external factors (e.g., hallucinations).

2.1.3 EEG resting-state connectivity findings in SZ: A brief overview

Alterations in RS networks have been noted across many EEG studies in psychiatric populations. Two recent reviews by Hasey and Kiang (2013) and Maran et al. (2016) have thoroughly overviewed EEG findings on local and long-range oscillatory synchronization in SZ patients during rest. In the following, we briefly summarize the main RS EEG findings in SZ patients, in

terms of alterations in spectral power (i.e. local synchrony) and changes in connectivity (i.e. long-range synchrony).

2.1.3.1 EEG Power modulations (local synchrony)

Among other alterations, enhanced gamma activity has been found with EEG over various brain regions in SZ (Venables et al., 2009; Gandal et al., 2012; Andreou et al., 2015; Di Lorenzo et al., 2015; White and Siegel, 2016), such as the auditory cortex (Northoff and Duncan, 2016), and the left parietal and fronto-temporal areas (Andreou et al., 2014; Mitra et al., 2015). However, decreased high gamma power (> 70 Hz) has also been noted over the right temporo-parietal brain areas and midline region (Umesh et al., 2016). With respect to lower frequency bands, a number of meta-analyses have noted increased activity in theta and delta frequency bands (Boutros et al., 2008; Venables et al., 2009; Kam et al., 2013; Narayanan et al., 2014; Di Lorenzo et al., 2015), as well as in beta-band over fronto-central areas (Narayanan et al., 2014). Moreover, while a few EEG studies show decreased RS alpha activity in SZ (e.g., in frontal lobe, Sponheim et al. 1994), a recent review found several publications revealing an increase in power in alpha-band in patients compared to controls in frontal regions (Northoff and Duncan, 2016). As mentioned by Maran et al (2016), the discrepancy between these findings could relate to differential spatial distribution of power changes.

2.1.3.2 EEG Connectivity (long-range synchrony)

A growing number of EEG studies are also investigating how connectivity patterns between different brain regions are altered in SZ during RS. One research group compared SZ patients with positive symptoms to those with predominantly negative symptoms, as well as healthy controls (Strelets et al., 2002). The RS portion of the EEG study showed both subgroups of SZ patients to lack interhemispheric connections. Patients with positive symptoms had an additional connection between right temporal and parietal lobes that was not present among control subjects in the 20-40 Hz frequency range (Strelets et al., 2002). Using coherence, a study found enhanced connectivity between centro-occipital brain regions within delta-band (2.0-3.5 Hz) in SZ (Wada et al., 1998), while another observed increased coherence in lower alpha frequency range (8–10 Hz) in centro-temporal, and upper alpha frequency (10–12 Hz) in centro-parietal and parietal-temporal regions (Kam et al., 2013). A recent study by Ford et al (2016) used simultaneous resting fMRI

and EEG on subjects and observed increased connectivity patterns within the DMN (< 30 Hz) in SZ compared to controls (Ford et al., 2016). Moreover, within the beta frequency band (13-20Hz), a longitudinal study found an initially diminished coherence between the left frontal and temporal electrodes to increase with treatment and improvement in positive symptoms (Higashima et al., 2007). Similar to what is often reported in RS fMRI, increased connectivity in the right frontal lobe area has been observed among drug-naïve SZ patients in gamma (30-50 Hz) frequency-band (Kikuchi et al., 2011), as well as between inferior frontal, orbitofrontal, temporal and inferior parietal areas (Andreou et al., 2015). Interestingly, two studies reported connectivity patterns opposing the above findings. Specifically, drug naïve patients were observed to display diminished alpha power, enhanced delta power, and non-discriminating beta and gamma rhythms in patients compared to controls (between frontal lobe sensors: Tauscher et al. 1998; between frontal and posterior sensors: Lehmann et al. 2014).

Taken together, findings from RS fMRI and EEG in SZ patients show a range of converging pathological alterations both in local activity and in inter-areal interactions between and within RS networks.

2.1.4 Resting-state MEG findings in Schizophrenia

A PubMed search of the key words "MEG + schizophrenia + resting" yielded 24 studies, 9 of which were relevant addition to this review. Nine additional MEG studies reporting on local rhythmic abnormalities were found through cross-referencing and the use of alternative search engines (Google Scholar).

In this section, we review all MEG-based RS studies in SZ. We first present MEG results of local synchrony (power) and follow-up with alterations in long-range oscillatory coupling (connectivity) between different brain regions.

2.1.4.1 Altered patterns of resting-state MEG oscillatory power in SZ

A summary of local neural oscillatory changes in SZ based on resting-state MEG studies can be found in Table 1.

First, the paper by Rutter et al (2009) used synthetic-aperture magnetometry (SAM) to estimate power source distribution. They found that both patients and their unaffected siblings had reduced gamma power (30-70 Hz) in the posterior medial PFC compared to controls (Rutter et al., 2009). In a subsequent study, Rutter and colleagues noted similar oscillatory behavior in SZ patients, but this time in the posterior part of their medial parietal cortex (Rutter et al., 2013). Similarly, Kissler et al (2000) found an overall reduction in high-gamma (61-71 Hz) frequencies in the areas of the fronto-temporal, posterior temporal and occipital lobe compared to age-matched controls (Kissler et al., 2000). Moreover, high beta (21-29 Hz) power was observed to be overall far superior in patients than in controls, regardless of the brain region (Kissler et al., 2000).

A more recent paper by Kim et al. 2014 found a significant increase in local synchronizations in theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz) and gamma (30-50 Hz) band frequencies in the posterior regions of the DMN (left posterior cingulate cortex) of patients compared to controls, as well in the left medial PFC in alpha and beta bands, during RS. Of note, power modulations in gamma in the medial PFC correlated with SZ patients' positive symptoms (e.g., hallucination, delusions; Kim et al. 2014).

Chen et al (2016) confirmed these findings about slow-wave patterns with a new source-modelling technique, vector-based spatio-temporal analysis using minimum norm on anatomical MRI. The authors observed enhanced activity in delta (1-4 Hz) and theta (4-7 Hz) frequency bands over right temporo-parietal and frontal brain regions (Chen et al., 2016). Frontal delta power correlated with patients' negative symptoms.

A number of older studies used a measure of dipole density to examine the distribution of different frequency bands. The article by Rockstroh and colleagues (2007) examined properties of delta-band oscillations during RS in three groups of subjects: healthy controls, SZ/schizoaffective patients, and mood disorder patients (consisting mostly of depressed individuals). Compared to healthy controls, the SZ/schizoaffective group displayed abnormally high delta (0.5-4 Hz) activity in the central and frontal areas of the brain (Rockstroh et al., 2007). Interestingly, the mood disorder group had less slow-wave activity compared to those of controls in these brain areas. A

similar study was previously conducted by Wienbruch et al (2003), where SZ patients were compared to depressed patients and healthy controls. Yet again, increased delta dipole density was observed in SZ, and decreased density in affective patients compared to healthy controls, which correlated with positive clinical symptoms such as hallucination/delusion (Wienbruch et al., 2003). However, unlike Rockstroh et al (2007), this difference was more important over the temporal and parietal brain regions. These papers offer interesting insight on the type of electrophysiological distinctions that can be made between the two diagnostic groups using RS MEG. Fehr et al (2001, 2003) and Sperling et al (2002, 2003) also found the density of dipoles generating delta (1.5-4 Hz) and theta (4-8 Hz) frequency bands to be superior in SZ patients compared to healthy controls over temporo-posterior (Sperling et al., 2002; Fehr et al., 2003), and frontal regions (Fehr et al., 2001). Moreover, changes in slow-wave density in these areas correlated with patients' negative symptoms (Fehr et al., 2003) and positive symptoms (Fehr et al., 2001; Sperling et al., 2002, 2003).

Three studies evaluated the effect of antipsychotics on local changes in RS synchronization patterns in SZ patients. Cañive et al (1996) found that both medicated and unmedicated patients displayed lower alpha-band power and peak frequency than controls (Cañive et al., 1996). In a follow-up study, delta, theta and alpha-band power and frequences were found to be diminished in patients at baseline (Cañive et al., 1998). After 8 weeks of ariprazole treatment, delta and theta levels were rescued, but alpha-band alterations remained unchanged. Next, in an all-male group of patients, Sperling et al (1999) observed differential changes in oscillatory patterns linked to typical and atypical antipsychotics. Specifically, beta-band power (12.5-30Hz) was increased in the temporoparietal region only by clozapine, while patients treated with haloperidol and healthy controls had dipole distribution concentrated centrally (Sperling et al., 1999).

Lastly, a number of interesting papers have reported MEG RS findings *during which* subjects were experiencing hallucinations. Using a dipole approach, Reulbach et al (2007) observed an increased number of dipoles and a dipole density maxima in the 2-6 Hz frequency band at rest. During auditory hallucinations, specifically, patients exhibited enhanced beta-band (12.5-30 Hz) activity over frontal and temporal brain regions (Reulbach et al., 2007). Moreover, an older case study by Ropohl et al (2004) observed similar increases in beta-band activity (12.5-30 Hz) over the left auditory cortex; an oscillatory pattern that was not present in resting healthy controls (Ropohl et

al., 2004). Finally, an interesting MEG case report of a young SZ patient with newly emerged auditory hallucinations found that the subject had bursts of theta (4-8 Hz) activity in the left superior temporal lobe and auditory association cortex *during* auditory hallucinations (Ishii et al., 2000). This pattern of theta oscillations differed from the steady behavior observed when the subject was not experiencing auditory hallucinations (as indicated by a button press).

Taken together, RS findings from both MEG and EEG-based power analyses show that SZ patients exhibit local alterations in oscillatory patterns across the frontal lobe and DMN, temporo-parietal lobes, sensory networks, CEN, and hippocampus. In particular, altered modulations in gamma-band and abnormally enhanced slow-wave oscillations are observed across modalities. These appear to be partially normalized with pharmacological treatment. Interestingly, auditory hallucinations seem to bring about a beta-band specific surge of power over temporal regions. Clinical correlations of these altered power levels are still up for debate, with some studies finding associations to positives (Fehr et al., 2001; Sperling et al., 2002; Wienbruch et al., 2003) and others to negative symptoms (Fehr et al., 2003; Chen et al., 2016) for different brain regions.

It is noteworthy to mention that the enhanced presence of EEG or MEG delta-band oscillations in these brain regions have been associated with clinical symptoms and cognitive deficits in both neurological (Tanaka et al., 1998; de Jongh et al., 2003; Spironelli et al., 2011) and psychiatric populations (e.g. in SZ patient, on and off medications, Rockstroh et al. 2000; Fehr et al. 2001; Wienbruch et al. 2003). While these findings are correlational in nature, it has been proposed that slow-wave activity might be associated to the neurobiological disruption of neural network functioning in SZ (Wienbruch et al. 2003). Delta modulations have also been reported in the power spectrum of awake healthy controls (e.g., during cognitive tasks, Harmony 2013; Wang et al. 2016; or sensory processing, Schroeder and Lakatos 2009). Although the distinction between normal and pathological slow-wave activity is not entirely understood, it is possible that different generators are involved, and that the amplitude and/or peak frequency of delta oscillations differ between healthy and SZ populations (Rockstroch, 2000; Wienbruch et al., 2003). Recently, a study used a rat-model of SZ to propose that the altered functioning of NMDA receptors could be the underlying mechanism of atypical delta-wave activity in this population (Kiss et al. 2011).

TABLE 1: OVERVIEW OF MEG RESTING-STATE FINDINGS ON CHANGES IN LOCAL POWER IN SUBJECTS WITH SCHIZOPHRENIA.

Paper	Frequency Range (Hz)	Methods	Patients	Controls	Main findings
(Cañive et al., 1996)	n/a	• Sensor-space Average power • 5min eyes-closed	• 19 SZ • (11 unmedicated)	• 10 controls	• ↓ α power and peak frequency in SZ compared to controls • Compared to medicated patients, one unmedicated showed epileptiform sharp waves, 4 showed abnormal slow waves.
(Cañive et al., 1998)	n/a	• Sensor-space • Dipole modeling	• 5 SZ	• 10 controls • age-matched	• ↓ δ, θ, α power and peak frequency in SZ compared to controls. • 8 weeks of ariprazole treatment ↑ δ and θ levels, but α remained unchanged. • Dipoles were localized primarly to temporal and parietal brain areas.
(Sperling et al., 1999)	2-6 α: 7.5-12 β: 12.5-30	• Dipole density • PCA	• SZ	• Controls	• Treatment with clozapine ↑ absolute dipole values in β-band in the temporoparietal region in SZ • SZ treated with haloperidol and un-treated healthy controls had dipoles concentrated centrally
(Kissler et al., 2000)	α: 8–12 β1:13–20 β2: 21–29 γ1: 30–45 γ2: 46–60 γ3: 61–71	• Power differences at sensor level • 5min eyes-open	• 15 SZ • 11 males • mean age 30.2 ± 6.5	• 15 controls • 11 males • mean age 35.8 ± 9.4	• ↓ γ3 power in SZ over fronto-temporal areas, posterior temporal lobe and occipital lobe compared to controls • ↑ β2 power in SZ compared controls across all brain regions
(Ishii et al., 2000)	δ: 0.9–4 θ: 4–8 α: 8–13 β: 13–25 γ: 25–60 all: 0.5-100	• Sensor-space estimation using SAM • 10s prior to button press and 10 s after a button press. At least 8	• 1 SZ • male • age: 28 yrs old	• n/a	• Burst of θ observed in left superior temporal lobe and auditory association cortex during AH • With reduction in AH vividness 7 months later, θ activity disappeared.

		episodes of AH recorded each session			
(Fehr et al., 2001)	δ: 1.5–4 θ: 4–8	• Source-space power estimated with Dipole density, MNE • 5min eyes-open	• 28 SZ • 22 males • mean age: 30.9 ± 9.6	• 20 controls • 15 males • mean age: 34.4 ± 11.3	• ↑ density of dipoles generating δ and θ in SZ compared to healthy controls over temporo-posterior areas. • Patients' positive symptoms appeared to be related to slow oscillations over frontal, parietal, and right hemispheric brain areas
(Sperling et al., 2002)	slow: 2-6 fast :12.5–30	• Dipole density plot • ECD • 10min eyes-closed	• 40 SZ • 23 male • mean age: 36.5 ± 3.9	• 30 controls • 15 males • mean age: 37.7± 4.0	• ↑ density of dipoles generating both slow and fast oscillatory activity in SZ compared to healthy controls over temporo-posterior areas. • Gender differences were observed in the spatial distribution of dipoles.
(Fehr et al., 2003)	δ: 1.5–4 θ: 4–8	• Single ECD model • Dipole density • 5min eyes-open	• 30 SZ • 18 males • mean age: 31.6± 8.9	• 17 controls • 15 males • mean age: 32.4± 11.2	• ↑ density of dipoles generating δ and θ in SZ compared to healthy controls over temporal and parietal areas.
(Sperling et al., 2003)	slow:2–6 fast: 12.5–30	• Dipole density plot • ECD • 10min eyes-closed	• 20 SZ • 10 males • mean age: 37.5 ± 3.4	• 20 controls • mean age: 34.6±3.4	• β-band density in the left temporoparietal region correlated with positive and negative symptoms, particularly in female patients. • In males, β-band dipole density in right temporoparietal region correlated with delusion.
(Wienbruch et al., 2003)	δ: 1.5–4 θ: 4–8	• Single ECD model • Dipole density • 5min eyes-open	• 29 SZ • 17 males • mean age: 31.6±8.9	• 18 controls • 16 males • mean age: 33.1±13.1	• ↑ δ dipole density in SZ compared to healthy controls and mood disorder patients over temporal and parietal brain regions. • This correlated with positive clinical symptoms

(Ropohl et al., 2004)	Slow: 2–6 β:12.5–30	• Dipole distribution plot, PCA • 10min	• 1 SZ • male • age: 33 yrs	• 13 controls • all male • mean age: 31.3 ± 4.7	• ↑ β dipoles observed over the left superior temporal cortex in SZ but not in controls
(Reulbach et al., 2007)	Slow: 2–6 β:12.5–30	• Spatial distribution of dipoles estimated using 3-D convolution with a Gaussian envelope • Dipole density plot	• 16 SZ • 9 male • 8 with AH • mean age: • 33 ± 2.8 year	• 8 controls • 4 males • mean age: 35 ± 8.2	• ↑ number of dipoles and dipole density maxima in 2-6 Hz • During AH, patients exhibited more ↑ β dipoles and dipole density maxima, then patients without AH • In SZ, all oscillations were mostly over the superior temporal gyri • Patients with AH had dipoles over left superior temporal gyrus, as well as dorsolateral PFC.
(Rockstroh et al., 2007)	δ: 1.5–4	• Single ECD model • ASWA/dipole density • 5min eyes-open	• 76 SZ or SA • 62 males • mean age: 29.12 ± 8.0	• 116 controls • 59 males • mean age: 28.95 ± 10.16	• ↑ ASWA in SZ/SA group compared to controls over central and frontal areas.
(Rutter et al., 2009)	δ: 0.9–4 θ: 4–8 α: 8–14 β: 14–30 γ: 30–80 super- γ: 80–150	• Source-space power estimated with SAM • Eyes-closed	• 38 SZ • 27males • mean age: 31.2 ± 9.8	• 38 controls • 27 males • mean age: 32.5 ± 10.8 • 38 U.S. • 11 males • mean age: 37.2 ± 11.3	• ↓ γ power in the posterior medial PFC in SZ patients and their US compared to controls • SAM power was superior in controls across all frequency bands compared to US.

(Rutter et al., 2013)	θ: 4–8 α: 8–14 β: 14–30 γ: 30–80	• Source-space power estimated with SAM • 4min eyes-closed	• 20 SZ • 14 males • mean age: 31.2 ± 10.9	• 20 controls • 14 males • mean age: 31.3 ± 10.8	• ↓ SAM γ power in SZ in precuneus, cuneus and posterior medial parietal cortex compared to controls. • None of the frequency bands survived multiple comparisons
(Kim et al., 2014)	θ: 4–7 α: 8–12 β: 13–30 γ: 30–50	• Source-space power estimated with sLORETA • 2.5 min eyes-open	• 20 SZ • 16 males • mean age 22.8 ± 3.9	• 20 controls • 14 males • mean age 22.1 ± 2.0	• ↑ θ, α, β power in SZ compared to controls in posterior cingulate cortex.
(Chen et al., 2016)	δ: 1–4 θ: 4–7	• Source-space amplitude estimated with VESTAL • 5min eyes-closed	• 41 SZ • 34 males • mean age: 37.63 ± 12.09	• 37 controls • 27 males • mean age: 38.92 ± 11.13	• ↑ δ and θ activity over temporo-parietal and frontal brain regions in SZ compared to controls. • Frontal lobe δ power correlated with patients' negative symptoms.

Table 1 - caption: Overview of MEG resting-state findings on changes in local power in subjects with Schizophrenia. Abbreviations: ASWA = Abnormal slow-wave activity, DICS = Dynamical Imaging of Coherent Sources, ECD = Equivalent current dipoles, MNE = minimum-norm estimate, MSBF = multiple source beamformer, PCA = principal component analysis, SA = schizoaffective, SAM = synthetic-aperture magnetometry, SZ = schizophrenia, U.S. = unaffected sibling, VESTAL = vector-based spatio-temporal analysis.

2.1.4.2 Altered resting-state MEG connectivity patterns in SZ

To date, six studies have used MEG RS paradigms to examine inter-areal synchronizations in SZ; these are summarized in Table 2.

First, using imaginary coherence (IC; Notle, 2004) within alpha frequency bins (peak power density centered on ≈ 10 Hz) in source-space, Hinkley et al (2011) observed that SZ subjects had altered local connectivity in several brain regions. Specifically, compared to the rest of the brain, patients displayed enhanced local connectivity in the right PFC and the occipital lobe (medial occipital gyrus, right inferior frontal gyrus), and reduced connectivity within the left dorsolateral PFC, the right superior temporal gyrus and the precentral gyrus compared to controls (Hinkley et al., 2011). Interestingly, medication dose was not a factor in global imaginary coherence connectivity in patients.

Second, Bowyer and colleagues (2015) studied coherence, the linear correlation between the amplitude of two signals, within brain areas that have been thought to have unusual activity in SZ patients (i.e. seeds placed in the following regions: dorsolateral and anterior PFC, orbitofrontal cortex, anterior cingulate cortex, frontal gyrus) (Fornito et al., 2009; Butler et al., 2012). The results of their preliminary ICA-based research in source-space, within the frequency range of 3-50 Hz, demonstrated that patients had higher coherence scores than controls across all these regions of interest. The authors hypothesized that their findings might be reflective of SZ individuals' over-recruitment of frontal brain areas.

Next, Zhang et al (2015) used phase-locking value (PLV) in sensor-space to investigate the inter-dependency of signals within and between regions of interest. The overall pattern of findings indicated that SZ patients had reduced PLV values compared to controls, with the largest differences residing between the right parietal and right central areas (0.5-8Hz), and right occipital and right parietal area in 1-4 Hz (Zhang et al., 2015).

Houck et al (2016) paired RS fMRI data with RS MEG. While different patterns of connectivity were observed between the two neuroimaging modalities, both revealed significant differences

between the SZ and control groups. Overall, the authors observed enhanced functional connectivity in visual networks during resting-fMRI, while frontal networks were enhanced in resting-MEG. Specifically, using pairwise correlations in network (ICA component) on time-series across all frequency bands, the RS MEG condition revealed enhanced connectivity between the regions of the dorsal ACC and superior frontal brain areas in SZ, as well as between frontal and perisylvian regions, while the connectivity between PCC and the precuneus were reduced, compared to controls. In beta-band (16-29 Hz) specifically, hyperconnectivity was observed in SZ compared to controls between the frontal lobe and cerebellum, the frontal lobe and the DMN, and the frontal and auditory resting networks. Interestingly, RS-fMRI showed control subjects to have overall increased connectivity compared to patients. This study underlines the importance of combining neuroimaging modalities to obtain maximal information.

Robinson and colleagues (2015) used symbolic mutual information (SMI) in source-space to calculate the dependence between two signals. This non-parametric measure of signal complexity, measuring shared information between pairs of voxels, was computed from the probability of occurrence of their symbolic states (Kraskov et al., 2004). Using this tool, long-range hyperconnectivity was observed between the medial PFC (seed) and part of the saliency network (dorsal ACC). The authors also mention that SZ patients had local-range connectivity in the frontal part of their PFC that was superior to those of control subjects, as indexed by higher SMI scores (Robinson and Mandell, 2015). However, patients' long-range connections to the lateral part of the PFC was weaker than those of control subjects. A follow-up on this study would be interesting in order to capture the details (e.g., frequency bands) of the altered long-range connections in SZ.

Finally, Rutter et al (2013) evaluated RS functional connectivity in SZ using coherence in MEG source-space. Additionally, graph theory metrics (Bullmore and Bassett, 2011) characterized several global network properties, such as small-worldness and path length. However, group differences in region-to-region and global graph metrics failed to reach statistical significance, after multiple comparisons (Rutter et al., 2013). Nevertheless, compared to controls, SZ patients did show a trend towards enhanced coherence between frontal gyrus and the rest of the brain in theta (4–8 Hz) and alpha (8-14 Hz) frequency bands, along with diminished coherence between medial parietal regions and all other voxels of the brain in the gamma (30-80 Hz) band.

All in all, current RS MEG findings in the SZ population show deficient connectivity patterns between and within different resting state networks (DMN, CEN, Saliency) and sensory areas (visual, auditory). In turn, these appear to be reflective of patients' positive and negative symptoms, possibly due to faulty information processing. Figure 4 illustrates the above RS MEG findings on connectivity alterations in SZ (specifically synchronizations between a brain region and the rest of the brain).

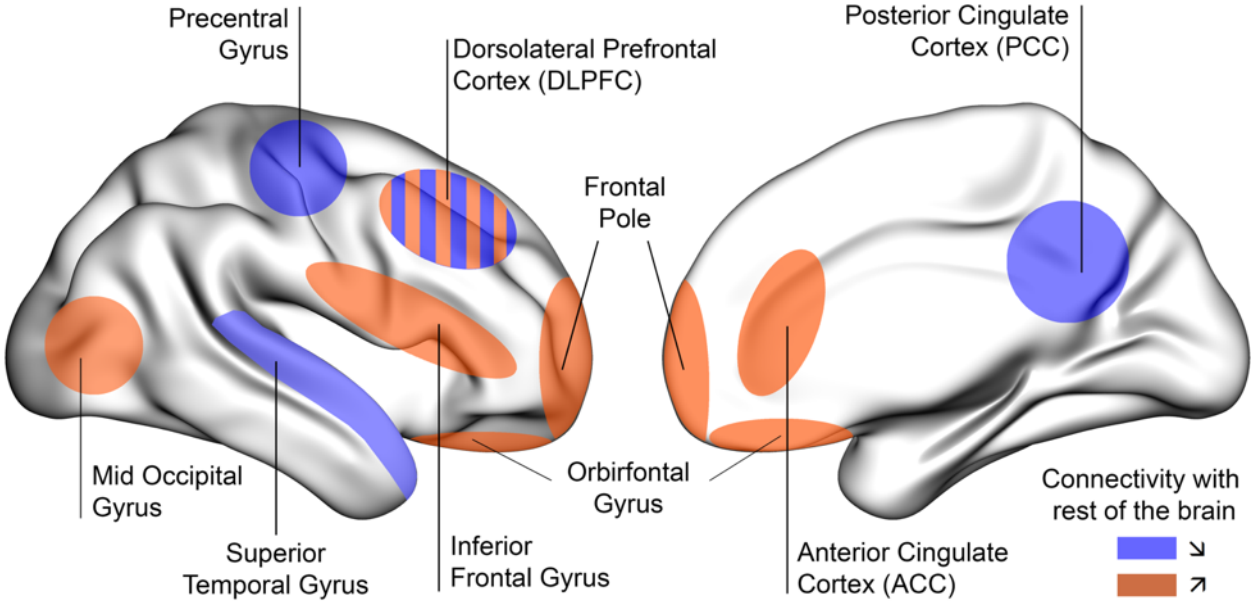


FIGURE 4: SCHEMATIC OVERVIEW OF THE KEY BRAIN REGIONS THAT SHOW ABNORMAL CONNECTIVITY PATTERNS IN SUBJECTS WITH SCHIZOPHRENIA.
Schematic overview of the key brain regions that show abnormal connectivity patterns in subjects with schizophrenia (SZ). Here, we show areas for which there is resting-state MEG evidence indicating that these areas have atypical long-range connections with the rest of the brain in patients compared to healthy controls. Brain regions colored in orange represents loci that have enhanced connections with the rest of the brain, and blue represents loci with decreased connections. Details of these findings can be found in Table 2.

TABLE 2: OVERVIEW OF MEG RESTING-STATE FINDINGS ON CHANGES IN LONG-RANGE OSCILLATORY CONNECTIVITY PATTERNS IN SUBJECTS WITH SCHIZOPHRENIA

Paper	Frequency Range (Hz)	Methods	Patients	Controls	Main findings
(Hinkley et al., 2011)	α: 8-12	• Imaginary coherence • Source-space estimation using Nutmeg software • 4min eyes-closed	• 30 SZ • 23 males • mean age: 38.4 ± 11.1	• 15 controls • 11 males • mean age: 43 ± 12.2	• ↑ connectivity compared to controls in medial occipital gyrus in the left hemisphere, and in the right IFG • ↓ connectivity within the left dorsolateral PFC and the precentral gyrus. • Alterations correlated with psychosis, depressed mood, and impaired cognition.
(Rutter et al., 2013)	θ: 4–8 α: 8–14 β: 14–30 γ: 30–80	• Coherence • Graph theory • Source-space estimation using SAM beamforming • 4min eyes-closed	• 20 SZ • 14 males • mean age: • 31.2 ± 10.9	• 20 controls • 14 males • mean age: • 31.3 ± 10.8	• No significant differences found between SZ and controls using coherence or graph theory metrics • SZ showed trend towards ↑ mean connectivity between frontal gyrus and the rest of the brain in θ and α bands, and ↓ between PPC sand the rest of the brain in γ-band.
(Bowyer et al., 2015)	3-50	• Coherence • Source-space estimation using ICA, MR-FOCUSS • 10min eyes-open	• 12 SZ • 10 males • mean age: 32 ± 8.8	• 12 controls • males • mean age: 27 ± 6.5	• ↑ coherence levels compared to controls in frontal pole cortex, dorsolateral PFC, orbitofrontal cortex, and the ACC.
(Robinson and Mandell, 2015)	n/a	• Symbolic mutual information (SMI) • Source-space	• 15 SZ • 10 males • age range: 20–45	• 14 controls • 5 males, • age-range: 19–36	• ↑ SMI values compared to controls in rostral PFC for short-range connections. • ↓ connectivity for long-range connections to lateral PFC.

(Zhang et al., 2015)	δ: 1–4 θ: 4–8 α: 8–12 β: 12–30 γ: 30–50	• Phase-lag value (PLV) • Sensor-space • 4min eyes-open	• 14 SZ • mean age: 27.6 years	• 22 controls • mean age: 27.6 years	• ↓ PLV overall compared to controls. • The α spectral band had the highest PL values. • The largest PLV difference was in the right frontal region.
(Houck et al., 2016)	δ: 1–4 θ: 5-9 α: 10-15 β: 16–29	• Zero-lag cross-correlations • Source-space estimation using beamformer and group spatial ICA • 6min eyes-open	• 44 SZ • 37 males • mean age: 37. 3 ± 13.9	• 47 controls • 34 males • mean age: 35.2 ± 11.8	• ↑ correlation within the dorsal ACC/superior frontal areas, ↑ between frontal brain areas and perisylvian regions in SZ, ↓ correlation within the PCC/precuneus region, compared to controls, across all frequency bands. • In β, ↑ between the frontal lobe and cerebellum, the frontal lobe and the DMN, and the frontal and auditory networks.

Table 2 - caption: Overview of MEG resting-state findings on changes in long-range oscillatory connectivity patterns in subjects with Schizophrenia. Abbreviations: ACC = anterior cingulate cortex, IFG = inferior frontal gyrus, PCC = posterior cingulate cortex, PFC = prefrontal cortex, PPC =posterior parietal cortex, TG= temporal gyrus, SZ = schizophrenia.

2.1.4.3 Strengths and limitations of resting-state MEG studies in SZ population

Although most of the reviewed SZ studies were conducted in source-space, one was analyzed at the sensor-level (Zhang et al. 2015). However, this paper had the strength of using an automatic classification algorithm (Support Vector Machine) to determine the connectivity features that best differentiate SZ patients from controls. Exploring key connectivity features in source-space using machine-learning approaches could be a promising venue for future studies.

Moreover, while Hinkley et al (2011) limited the frequency range that they investigated to the alpha-band, the paper's strength lies in its use of imaginary coherence to measure functional connectivity. The other resting-state MEG studies discussed in section 2.1.4.2 used linear metrics potentially prone to field spread issues (Bowyer et al., 2015; Robinson and Mandell, 2015; Zhang et al., 2015; Houck et al., 2016). With respect to sample size, Zhang et al (2015), Robinson et al (2015) and Bowyer et al (2015) are limited by their relatively small cohorts. While, the authors mention that their source-space articles show preliminary results, it is clear that elaboration of their findings with larger patient and controls cohorts could help uphold the altered connectivity patterns observed.

Rutter et al (2013) illustrated the promise of the use of graph theoretical metrics for the quantification of alteration in neural networks in SZ. While they did not find statistically significant group differences, global alterations in SZ patients have been observed in previous RS fMRI (Bassett et al., 2008; Liu et al., 2008; Bullmore and Sporns, 2009; Yu et al., 2012; Cheng et al., 2015; Su et al., 2015) and RS EEG studies (e.g. Micheloyannis et al. 2006; Rubinov and Sporns 2010). Hence, future explorations of graph theory with RS MEG are needed to clarify these inconsistencies.

The correlational findings between pathological symptoms and connectivity patterns observed in most of the reviewed literature (e.g. Fehr, 2001; Sperling 2002; Hinkley 2011) are not always consistent across studies. This variability could relate to either methodological issues in MEG measurement or to a nosographic (i.e. classification) problem. Indeed, each symptom could be considered as a heterogeneous set of more basic sub-processes, which could be addressed by assessing specific domains and constructs (e.g., cognition, arousal/inhibitory systems) as

suggested by the Research Domain Criteria framework. Although it is still in its early days, the application of this novel approach in psychiatry (e.g., hallucinations, Ford et al. 2014) is promising. An in-depth discussion of the relevance of domain-oriented classification goes beyond the objective of the current review.

Finally, it is important to note that the findings about how changes in intrinsic brain rhythms relate to positive and negative symptoms are correlational in nature. In the future, SZ models and stimulation paradigms (e.g. TMS) could be used to further elucidate the directional link between alterations in RS connectivity patterns and patients' symptoms. These could confirm to which extent network changes give rise to clinical symptoms (Stephan et al., 2009) or to domain-specific deficits (Morris and Cuthbert, 2012). These questions will be central to future studies in the field of psychiatry.

2.1.4.4 Bridging findings between resting state and task-based paradigms

The literature on MEG connectivity in SZ patients contains studies that use sensory and cognitive tasks to explore connectivity patterns. Some of the results arising from these task-based investigations corroborate what is observed in resting-state studies.

The finding of decreased connectivity between the right parietal and occipital lobes that was shown at rest (Zhang et al. 2015) has also been observed during a task-based study. Fujimoto et al. (2013) examined the correlation between SZ patients' symptoms and imaginary coherence (IC) between different brain regions during an auditory oddball paradigm. Hallucinatory behavior correlated positively with decreased connectivity between left occipital and right fronto-parietal areas (Fujimoto et al., 2013). Another finding from the RS MEG study by Zhang et al. (2015) regarding the involvement of the occipital lobe was also observed in a task-based paradigm. Brookes et al (2016) conducted a visuo-motor task with SZ and control subjects, where participants were instructed to press a button whenever a visual stimulus of a grated square was presented. Using beamforming source localization, functional connectivity between various seeds and test brain regions were measured by examining the change in oscillatory envelope (i.e., amplitude) correlations. Of note, patients had reduced connectivity within certain nodes of the occipital lobe in alpha-band (8-13 Hz) frequencies. Furthermore, the strength of decreased synchrony correlated

with symptom severity. However, the decreased long-range synchronization between occipital and other brain regions occurred mostly in the theta-band frequency range.

Other alterations in long-range synchronization have been observed in SZ patients during the performance of a task, which have not found a parallel in resting-state studies. For instance, Fujimoto et al. (2013) found patients to display decreased connectivity between right temporal pole and left prefrontal lobe areas, which correlated with delusion score and conceptual disorganization scores in low-gamma. Similar decreased connectivity between these brain regions have also been observed during RS EEG recordings in SZ (Winterer et al. 2003), but have yet to be replicated in MEG at rest. Decreased connectivity in low and high-gamma frequency bands between left occipital lobe and right anterior PFC were also noted by Fujimoto et al. (2013). Moreover, compared to controls, SZ patients had decreased connectivity between the right intraparietal sulcus and the temporo-parietal junction during an attention task. Disruption in this pattern correlated with lower IQ scores in patients. The authors suggested that this finding highlights the importance of the fronto-temporal network in cognitive processes. Decreased gamma-band power has also been noted in patients during a working memory task over fronto-posterior brain areas (Popov and Popova, 2015). Lastly, using mutual information in source-space, SZ patients have been seen to have disrupted connectivity between the right amygdala and the primary and secondary visual cortices compared to healthy controls in a visual categorization task (Ioannides et al., 2004). However, most of the observed group differences were time-locked to different moments during task performance. Hence, it is possible that the above alterations in connectivity are specific to given tasks or, alternatively, to an intrinsic SZ biomarker that is only detectable via task-based paradigms. Future MEG studies will perhaps offer clarity on this issue.

2.1.4.5 Summary of resting-state connectivity findings across 3 neuroimaging modalities

Findings on the intrinsic connectivity patterns of SZ patients are heterogeneous. At this stage, it is thus difficult to obtain a consensus across fMRI, EEG and MEG on the neural connections that are consistently observed to be aberrant. Nevertheless, across the three neuroimaging modalities reviewed here, functional connectivity within the PFC is altered in SZ patients compared to controls. Moreover, cumulated RS fMRI and EEG studies have shown SZ patients to have decreased connectivity between frontal and temporal lobes, and enhanced connectivity between

central and occipital brain regions, while fMRI and MEG have observed hypoconnectivity between the parietal cortex and the occipital lobe. Electrophysiological studies also note altered connectivity between parietal and central brain regions, along with enhanced connections between temporal and parietal regions. Finally, a number of fMRI studies strongly show hypoconnectivity between the thalamus and the DMN, between the DMN and the CEN, and between the thalamus and the frontal lobe in general. Hyperconnectivity appears to take place in the thalamocortical pathway, particularly between the thalamus and sensorimotor areas. These loci could be linked to patients' hallucinatory/delusional symptoms.

While pharmacological treatment appears to be a modulating factor of the atypical local and long-range rhythmic behaviors, the direction of the effect is still unclear. Interestingly, some researchers have used pharmacological models of SZ to explore connectivity changes. For instance, a recent MEG study examined the effect of a sub-anesthetic dose of ketamine in healthy individuals (Rivolta et al., 2015). This compound seems to invoke changes that resemble the neurobiological portrait, as well as the positive and negative symptoms, of SZ, in both healthy individuals and animal models (Becker et al., 2003; Frohlich and Van Horn, 2014). Rivolta et al (2015) used transfer entropy in RS source-space data to examine directed long-range interactions in beta (13-30 Hz) and gamma (30-90 Hz) frequency bands in relation to ketamine administration. Transfer entropy (TE) quantifies the amount of information of a target that can only be predicted by knowing the past of the source (Schreiber, 2000). The TE analysis showed increased information transfer in a thalamo-cortical network after ketamine administration; after 2-4 weeks, subjects that were administered the active treatment displayed enhanced TE between the left medial temporal gyrus and the right inferior temporal gyrus (gamma to beta), the right inferior temporal gyrus and the left thalamus (beta to gamma), the left thalamus and the right visual cortex (gamma to beta), the right visual cortex and right precuneus (within beta band), right precuneus and left thalamus (beta to gamma), and left medial temporal gyrus and right thalamus (within gamma band). Beyond providing an interesting illustration of how ketamine may be used to model brain changes in SZ, the results of this study also highlight the potential of using directed and inter-frequency interaction measures to unravel oscillatory circuit dysregulations in SZ.

2.1.5 Methodological challenges and recommendations

As portrayed in this review, more MEG studies are needed to corroborate and extend previous reports, and thus reduce the existing heterogeneity between results of neuroimaging studies and across modalities. Some of these discrepancies might arise from methodological constraints. Indeed, several pitfalls and methodological limitations need to be taken into account when setting out to assess alterations in RS connectivity patterns in SZ with MEG. In the following, we describe the main technical challenges and we provide recommendations for future research in the field.

2.1.5.1 MEG connectivity estimation in SZ

Achieving a reliable estimation of inter-areal functional connectivity with MEG is a non-trivial task (van Diessen et al., 2015a). Most of the commonly used interaction measures (e.g. coherence or phase-locking value) can lead to artefactual coupling due to field spread (linear mixing in sensor space analysis) or signal leakage (in source space) (Schoffelen and Gross, 2009). Numerous MEG coupling measures have been proposed (e.g. Colclough et al., 2015; Hillebrand et al., 2016, 2012; O'Neill et al., 2015; Sakkalis, 2011), yet there is no real consensus as to which one provides the most reliable estimate of true cortical interaction. Furthermore, some methods are particularly suited for particular types of interaction phenomena (i.e. amplitude-amplitude, phase-phase, or phase-amplitude coupling, etc.). Unfortunately, the mechanistic properties of the cerebral interactions that are altered in SZ are not entirely understood. So, although several methods have been applied to MEG or EEG data, it is still up for debate which coupling technique (if any) is best suited to capture the pathological communication in SZ. Using different metrics on the same MEG data set might ultimately turn out to be the most reliable approach to settling this question. We recommend, for instance, the combination of complementary metrics such as phase-lag index (Stam et al., 2007; Vinck et al., 2011) and band-limited envelope correlations (Brookes et al., 2012; Hipp et al., 2012; O'Neill et al., 2015). In the absence of a specific hypothesis about a distinct phase-based or amplitude-based connectivity alteration, exploring both types of measures with the same data set provides a broader picture, leads to a more specific interpretation and reduces bias caused by arbitrary methodological choices. Agreement between phase-based and amplitude based analyses would increase reliability and confidence in the observed interactions. But discrepancies between the two measures would fine-tune the conclusions in terms of the underlying mechanisms. Alternatively, combining such standard linear metrics with non-linear measures (e.g. transfer

entropy) is also recommended. Again, unless one has a specific hypothesis, examining both linear and non-linear metrics increases the chance of identifying the nature of putative interactions (if the results differ) and increases the confidence in the robustness of the findings (if the results are consistent across methods). Naturally, exploring effective connectivity measures that capture the directionality of the coupling is of high interest. Most importantly, the pitfalls and strengths of the various techniques used need to be understood and reported with the results obtained.

2.1.5.2 From sensor to source-level analyses

Source-space connectivity measurements are essential to determine the neuroanatomical underpinning and functional role of the involved networks and, thereby, help bridge the gap between MEG and fMRI findings in psychiatry (Alamian et al., 2017a). Many electrophysiological studies in SZ still conduct their analyses in sensor-space. Choosing the most appropriate source reconstruction method to be used prior to source-level connectivity analysis is a difficult decision. The effect of different methods (such as beamforming and minimum-norm) on subsequent source-level coupling analyses is still poorly understood (Hincapié et al., 2016). Although we expect most families of source estimation methods (e.g. minimum-norm or spatial filters) to provide comparable results, it is important to understand the hypothesis and limitations of a chosen method and its parameters, and their impact on source-space connectivity estimations (Hincapié et al., 2016). However, the actual acquisition parameters and task-design might ultimately turn out to have a larger effect on the quality of connectivity estimation than the applied source estimation technique.

2.1.5.3 Reliability of MEG-based resting-state networks estimations

The stability and robustness of RS connectivity estimation, over time and across participants, are important factors that are often overlooked in MEG-based studies, both in healthy and clinical cohorts. Recent research has addressed the reliability of MEG RS connectivity metrics (Colclough et al., 2016) and its test-retest reliability (Garcés et al., 2016). Both inter- and intra-subject consistency of MEG RS network estimations have been investigated and it has been found that, while variability exists, seed-based and appropriate averaging techniques allow the comparison of subjects between and within groups (Wens et al., 2014). Furthermore, the SZ MEG resting-state studies reviewed here used recording lengths that varied between 4 and 6 minutes. Recently, Liuzzi et al (2016) found that recording duration has a critical effect on reproducibility of MEG RS

connectivity findings. Interestingly, the authors report significant improvements in repeatability when using ten minute-long recordings, compared to five minutes. Moreover, although five minutes might be considered a reasonable length, more data could be necessary in the case of patient populations, as more data loss is expected (e.g. because of more movement artefacts). In addition, Liuzzi et al. (2016) also found that the use of a foam head-cast improved reproducibility of results between sessions, insuring reproducibility of the estimation of connectivity patterns, as well as the accuracy of source reconstruction (Liuzzi et al., 2016). Finally, at least half of the MEG RS studies reviewed here was carried out with eyes open. If acquiring data with both eyes open and closed is not feasible, we suggest using eyes open with a fixation cross to minimize eye movements. Eyes closed RS is associated with strong alpha power increases and can induce drowsiness, with participants potentially falling asleep during the recording (Tagliazucchi and Laufs, 2014).

2.1.5.4 Contrasting controls and schizophrenia patients

Pathological alterations in signal amplitude can adversely affect the estimation of inter-areal connectivity in patients, and thereby lead to spurious group differences. This can occur because lower signal amplitudes result in lower signal-to-noise ratio (SNR). A good rule of conduct is to systematically estimate spectral power for the areas or channels involved in connectivity estimation and, if needed, control for the effect of amplitude across the two groups (e.g. using stratification techniques). In addition, increased head and body movement artefacts, eye blinks and saccades are common in patients and lead to poorer data quality. The rejection of contaminated segments during the data cleaning process will thus yield lower SNR in patient data compared to controls. Differences in SNR across two conditions or two populations are detrimental to spectral connectivity estimates. Hence, minimizing data rejection through the use of artefact correction techniques, such as independent component analyses (ICA), can be an efficient way to avoid such effects. This said, the differential application of ICA to the two groups also lead to differences that may bias connectivity findings and data interpretation. One way to address artefact-related SNR discrepancies between patients and controls is to acquire more data in patients or, alternatively, to use a subsample of data from the controls to achieve comparable SNR across the two groups.

2.1.5.5 Effect of age and medication on connectivity patterns in SZ

Schizophrenia patients are known to display heterogeneous symptomatic profiles. Thus, it can be difficult to untangle whether the source of connectivity differences are due to the illness itself or to other factors. Among a number of key variables, age and psychotropic medications are known to affect the synchronization of neural activity.

Critical connections in the brain, particularly those of the PFC, continue to develop through late adolescence. Developmental (e.g., early brain damage) and environmental factors can affect these patterns and give rise to some of the aberrant neural wiring of intrinsic neurophysiological networks that are observed in the SZ population (Carrion and Wong, 2012; Kolb et al., 2012; Grossmann, 2013; Baker et al., 2015). For instance, gamma-band oscillations appear to increase in the transition from adolescence to adulthood (Uhlhaas and Singer, 2010), thus disruptions of any type could affect high-frequency synchronizations. As discussed in the previous section, these rhythms are indeed affected in SZ. With increasing age, cognitive functions and the strength in connections across all populations decrease. However, it appears that it may affect SZ more aggressively, with patients showing steeper decline in some function than controls, such as abstract thought (Fucetola et al., 2000). Lastly, age of illness onset is also an important factor to take into consideration as early onset/pre-adolescence onset of psychopathologies typically correlate with worse prognosis and more severe clinical symptoms (Strober et al., 1988; Clemmensen et al., 2012).

The effect of pharmacological treatment on intrinsic neural circuitry has been under investigation for quite some time. Grey matter volume, anatomical connections and functional associations have all been found to be altered by antipsychotic treatment (Konradi and Heckers, 2001; Vita and De Peri, 2007; Nejad et al., 2012). Longitudinal MRI-based studies and reviews (Fusar-Poli et al., 2013; Ho et al., 2011) show that increased length and amount of antipsychotic treatment correlate with decreases in both grey and white matter volumes in patients. Other studies suggest that this volume reduction is more reflective of older treatment choice, and it could be spared by choosing atypical over typical antipsychotics (Scherk and Falkai, 2006). As clinical symptoms improve, functional connectivity between a number of affected brain regions appears to be restored with medication intake (e.g., Guo et al., 2016). For instance, fMRI studies have shown atypical

antipsychotics (e.g., aripiprazole, risperidol, olanzapine) to strengthen long-range connectivity between the striatum and the ACC, the dorsolateral PFC, hippocampus and anterior insula, as well as diminish connectivity between the striatum and parietal cortex (Sarpal et al., 2015). Connectivity between the DMN and the ventromedial PFC (Sambataro et al., 2010), as well as connectivity within a number of RS networks (e.g., CEN and salience network; Kraguljac et al. 2015), have also been enhanced after treatment with antipsychotics.

While some studies find no association between abnormal connections and the factors of age and medication (Nesvåg et al., 2008), it is important to untangle the differential effects of age, medication, as well as gender (e.g., Wienbruch et al. 2003), get to the basic neurophysiological nature of the illness and ensure that any differences observed between clinical and healthy populations are attributed to true alterations and not due to confounding variables (Bijanki et al., 2015). One way to do so is by conducting studies in drug-naïve and/or first-episode psychosis patients that have yet to be exposed to antipsychotics. Many fMRI (e.g., Lui et al. 2010; Ho et al. 2011; Sarpal et al. 2015; Guo et al. 2016), and EEG (e.g., Kikuchi et al. 2011; Andreou et al. 2014; Ramyead et al. 2016) studies have incorporated treatment-naïve patients in their protocols, but more MEG studies are needed (Bachmann et al., 2010; Roiser et al., 2013; Sun et al., 2013).

2.1.6 Discussion

In this systematic review, we provide a critical overview of current progress and limitations of MEG studies exploring oscillatory connectivity patterns in SZ populations, with a focus on RS data. In the following we discuss a number of closely related issues and questions that arise from this body of research.

2.1.6.1 Relevance of resting-state network analyses in psychiatric populations

Traditionally, neuroimaging paradigms have used tasks to study healthy, psychiatric or neurological populations (e.g., in SZ : Hamm et al. 2011; Haesebaert et al. 2013; Sun et al. 2013; Popov et al. 2014, 2015; Popov and Popova 2015; Liddle et al. 2016; Thuné et al. 2016). This approach is useful to investigate how information of various nature (e.g., emotional, physical, sensory, visual, cognitive, etc.) is processed (e.g., Edgar et al., 2008). It has long been known that, even in the absence of a specific task, the brain continually generates neural activity often referred

to as background, idling, ongoing or spontaneous activity. Yet, it is only in recent years that observing the brain during rest has become recognized as a useful way to study the fundamental organization of a person's brain and even differentiate patient populations from psychologically and neurologically healthy individuals (Fox and Greicius, 2010). A limitation of task-based experiments is that they require a response (e.g., button press, mental arithmetic, language processing) that typically affects the physical state of subjects, for instance, by bringing about unwanted movements that can induce artifacts in the signal and, in some case, adversely impact the signal to noise ratio. Moreover, task paradigms typically entail repeated trials and averaging in order to reduce the noise in the evoked-signal (Dawson, 1951) and consistently study how the brain activity is modulated during a given task. Although it can provide useful information, this type of analysis across trials (i.e., computing event-related potentials) could lead to a reduction in the richness of the information that resides within electrophysiological signals. Time-frequency approaches can be applied to task-based studies and may overcome this limitation. This said, all such findings focus on healthy vs pathological brain responses in a given behavioral context.

RS paradigms have the advantage of providing insight on the connectivity dysfunctions that are independent of context, and actually examine the core organization of psychiatric patients' brains. Test-retest reliability of RS fMRI experiments (ROI and voxel-based analyses) have been shown to be robust over time and across subjects. However, negative inter-areal correlations in fMRI produced less reliable test-retest outcomes (Shehzad et al., 2009). This finding could explain some of the differences found between studies.

RS is a baseline measure that provides the opportunity to dissociate neural correlates that are unique to psychopathologies (Fox and Greicius, 2010). Comparisons between the activation of task-based and rest-based networks have revealed a large amount of overlap (Di et al., 2013). A number of studies have even used RS data to predict task-based brain activity (e.g., Tavor et al. 2016). However, task-based paradigms appear to have superior information transmission and system integration compared to rest, with the thalamus being affected the most when switching between the two conditions (Di et al., 2013). One example of connectivity difference between rest and task, is local power modulations in gamma that have been seen to be enhanced during RS in SZ patients, but decreased during an induced, steady-state, sensory – auditory or visual - task (Uhlhaas et al., 2008; Wilson et al., 2008; Grent-'t-Jong et al., 2016).

Complimentary use of rest and task based paradigms is critical to examine the functional significance of the altered networks on a person's day-to-day life, in reaction to certain environments or stimuli (Bardouille and Boe, 2012). This is particularly true for psychopathologies that do not have distinct network organizations that are exceptionally different from healthy controls.

2.1.6.2 Advantages of MEG over fMRI for examining resting-state dynamics

A recent review investigated the relationship between MEG's magnetic signal and fMRI's BOLD signal, and found high frequency bands to positively correlate with BOLD, and low frequency bands to negatively correlate with BOLD (Hall et al., 2014). However, as mentioned in the introduction, there are a number of limitations in RS fMRI that are compensated by using MEG alone or in combination with MRI. The BOLD signal allows for an indirect observation of neural activity, while MEG directly measures neuronal magnetic primary currents and is reflective of a large population of neurons firing synchronously. The primary advantage of electrophysiological techniques such as MEG over fMRI is superior temporal precision, which allows the examination of oscillations that operate on short time scales. Indeed, due to the inverse relationship between temporal and spectral resolutions, higher temporal precision allows access to higher frequencies in the signal. Moreover, it has been suggested that proper information integration relies on cross-frequency coupling of oscillations in different brain areas (Jirsa and Müller, 2013). Indeed, there is an increasing interest in measures of cross-frequency coupling in the field of psychiatry (e.g., Moran and Hong 2011; Uhlhaas 2013). A few MEG studies have explored cross-frequency coupling in SZ population, during task-based paradigms. For instance, Sun et al (2013) performed cross-frequency coupling analyses on MEG data recorded during a visual task (perception of Mooney faces) and, more recently, Hwang et al. (2016) did the same with an inhibitory control task. This connectivity analysis has however yet to be applied to RS MEG data in this pathology. Globally speaking, the correspondence between local high-frequency activity (e.g., beta, gamma) and long-range low-frequency activity (e.g., theta, alpha) is thought to be a marker for healthy brain functioning, and alterations in this measure during a task (e.g., oddball) has allowed to distinguish psychiatric groups from controls (e.g., Allen et al., 2011). Hence, electrophysiological data, such as MEG, allows the investigation of oscillatory behavior that affects the intrinsic

organization of neural networks, as well as information processing related to overall functioning (e.g., Allen et al. 2011; Palva and Palva 2011).

However, any single neuroimaging modality is imperfect, and limited by a certain factor (e.g., spatial or temporal resolution). Hence, combining tools can enhance the richness of the collected information on both the signal of neural activity and brain structure, and allows for the uncovering of significant local or long-range networks that might go otherwise undetected (e.g., Patel et al. 2016; Baenninger et al. 2017). An illustration of the benefits of multi-modality is provided in the study by Cousijn et al (2015) where RS MEG and fMRI scans were conducted in healthy individuals with genetic risks of SZ. The reported results showed that enhanced hippocampal/PFC co-activation correlated with changes in the theta frequency band within the hippocampus (Cousijn et al., 2015). Hence, the fusion of structural MRI with MEG can help bridge the gap between electrophysiological measures of coupling and structural measures, such as DTI.

To date, there have been few attempts to characterize the electrophysiological counterparts of fMRI RS networks using MEG. Studies suggest that the apparent temporal stationarity of RS networks shows a rich structure both in the time- and frequency-domains. Indeed, MEG can not only replicate the RS networks seen with the BOLD signal, but also provide new information on the mechanisms underlying their interaction (De Pasquale et al., 2010; Brookes et al., 2011b, 2011a; de Pasquale et al., 2012; Hipp et al., 2012). Interestingly, there have been several reports that the MEG correlate of fMRI RS networks might be the coupled fluctuation of band-limited power envelope correlations in the alpha or beta frequency bands at slow time scales (0.1 Hz), measured between different RSN nodes (De Pasquale et al., 2010; Brookes et al., 2011b; de Pasquale et al., 2012; Hipp et al., 2012; Betti et al., 2013). The precise link between slow BOLD fluctuations and brain-wide modulations of the electrophysiological signals is an important topic of current investigation, and more research is needed to bridge neuroimaging modalities (Foster et al., 2016).

2.1.6.3 MEG vs EEG for resting-state studies in psychiatric populations

EEG signals directly measure the electrical potential generated by neuronal currents, arising via volume conduction, from the brain's gyri and sulcI (Lopes Da Silva, 2013). This signal is thought to be reflective of a large population of neurons firing synchronously to bring a measurable

postsynaptic potential, with contributions from both tangential and radial currents. Only the tangential component of the primary current contributes to the MEG signal (Lopes Da Silva, 2013). True radial sources with vanishing tangential components are however rare, in particular if one considers that active brain areas are generally spatially extended. MEG compensates for EEG signal's pitfalls (e.g., distortion by skull and skin conductance) as it is not affected by conductance. Consequently, source reconstruction, with techniques such as the boundary element model (BEM), is easier to perform with MEG. Specifically, in the case of BEM, at least 3 layers should be considered to solve the EEG forward model, while a single layer can be sufficient to solve the MEG forward model (envelope of the brain).

While on a practical basis, EEG might seem to be more appealing due to its low cost and portability, MEG's preparation time for data acquisition is far shorter than EEG. Indeed, scalp EEG paradigms require participants to sit still for 20-40 minutes while the cap is properly positioned and fastened onto the scalp, and electrode impedances are individually checked, a procedure that could be difficult to perform on restless, psychiatric, populations. While no reference is required for MEG set up, the machine's shielded room can however be distressing to individuals with psychotic/paranoid profiles. Furthermore, source localization (e.g. using MRI-based T1 anatomical scan) is still needed for both modalities.

It is important to note that is possible to combine MEG and EEG using simultaneous acquisition (e.g. Dale and Sereno 1993; Dubarry et al. 2014). A recent paper (Muthuraman et al., 2015) demonstrated that the combination of EEG and MEG signals is better than using either alone for source mean power, functional or effective connectivity measures.

2.1.6.4 Current and up-coming clinical application for MEG in SZ

As discussed in the Introduction, the core differences between SZ patients and healthy individuals are thought to involve alterations at multiple levels, including neural network dynamics, neurochemical changes, epigenetics (e.g., Lisman et al. 2012). Our understanding of the neural underpinnings of SZ could benefit from incorporating MEG techniques within clinical settings. Furthermore, MEG could assist in the improvement of parameter choices for neuromodulatory clinical interventions, such as TDCS and TMS. For instance, by identifying how key connectivity patterns are altered in this population, source-localized MEG findings could clue us in on the

frequency bands and brain regions that are optimal for successful treatment by transcranial stimulations (e.g., Thut et al. 2017).

There is also a rise in the use of machine-learning algorithms in neuroscience, and more recently in psychiatry. One way to make use of this innovation is by applying unsupervised clustering techniques to RS MEG data to identify patient sub-groups of SZ (as discussed in the review by Uhlhaas et al., 2017; and conducted by Koutsouleris et al., 2009, and Clementz et al., 2016). This in turn could help untangle the heterogeneous nature of current functional connectivity results. In other words, distinct sub-types of SZ might underline the different connectivity alterations observed in the SZ literature. Finally, future longitudinal RS MEG studies could help identify biomarkers for individuals at risk (e.g., genetic predisposition for psychosis) by capturing how the intrinsic neural networks of SZ patients evolve differently than those of non-psychotic, or healthy, individuals.

2.1.7 Conclusions

Global and local alterations in information processing appear to be an intrinsic property of the neurophysiology of SZ. The most pervasive findings speak of diffuse discoordination/disorganization of neural networks across the whole brain. Specifically, disrupted oscillatory modulations have been reported within the DMN, along with enhanced long-range connectivity between the thalamus and sensorimotor areas, and diminished connectivity between the thalamus and PFC, and within the frontal cortex. With respect to local synchronizations, consistent findings across EEG and MEG report atypically enhanced slow oscillations and diminished fast (gamma) oscillations. Some of these alterations in rhythmic brain activity in SZ correlate with patients' overt clinical symptoms, as well as their cognitive deficits. These results corroborate and extend previous studies that suggest that gamma activity is not simply aberrant in schizophrenia but reflects a specific neural integration/segregation imbalance. Likely occurring at the level of cellular communication, this segregation deficit affects the global functional connectivity architecture and hinders effective processing including cognitive performance.

While still in its early days, RS MEG has led to important clinical insights in numerous brain disorders and has become a promising tool for clinical and translational research in psychiatry

(Siekmeier and Stufflebeam, 2010; Williams and Sachdev, 2010; Alamian et al., 2017a; Uhlhaas et al., 2017). More specifically, connectivity studies are a fast growing sub-portion of the SZ literature. This review in SZ population linked new RS MEG findings about the fundamental organization of neural networks in SZ to those obtained with other neuroimaging modalities in the same population. The literature overview, as well as the methodological considerations and recommendations provided in the present article will hopefully provide useful insights to the scientific community and to newcomers to this promising research field.

2.2 Alterations of Intrinsic Brain Connectivity Patterns in Depression and Bipolar Disorders: A Critical Assessment of MEG-based Evidence

Abstract

Despite being the object of a thriving field of clinical research, the investigation of intrinsic brain network alterations in psychiatric illnesses is still in its early days. Because the pathological alterations are predominantly probed using functional magnetic resonance imaging (fMRI), many questions about the electrophysiological bases of resting-state alterations in psychiatric disorders, particularly among mood disorder patients, remain unanswered. Alongside important research using electroencephalography (EEG), the specific recent contributions and future promise of magnetoencephalography (MEG) in this field are not fully recognized and valued. Here, we provide a critical review of recent findings from MEG resting-state connectivity within major depressive disorder (MDD) and bipolar disorder (BD). The clinical MEG resting-state results are compared to those previously reported with fMRI and EEG. Taken together, MEG appears to be a promising but still critically under-exploited technique to unravel the neurophysiological mechanisms that mediate abnormal (both hyper- and hypo-) connectivity patterns involved in MDD and BD. In particular, a major strength of MEG is its ability to provide source-space estimations of neuromagnetic long-range rhythmic synchronization at various frequencies (i.e. oscillatory coupling). The reviewed literature highlights the relevance of probing local and inter-regional rhythmic synchronization in order to explore the pathophysiological underpinnings of each disorder. However, before we can fully take advantage of MEG connectivity analyses in psychiatry, several limitations inherent to MEG connectivity analyses need to be understood and taken into account. Thus, we also discuss current methodological challenges and outline paths for future research. MEG resting-state studies provide an important window onto perturbed spontaneous oscillatory brain networks and hence supply an important complement to fMRI-based resting-state measurements in psychiatric populations.

2.2.1 Introduction

2.2.1.1 Background

Over the last decade, research on the human brain has experienced an important shift in paradigm; the functional investigation of neuronal activity has moved from studying local mechanisms towards large-scale network organization. Unavoidably, this change in the examination of neural connectivity has reached the field of psychiatry. Until recently, most connectivity studies in psychiatric patients were predominantly carried out using functional magnetic resonance imaging (fMRI). The findings from these studies generally indicate the presence of structural and/or functional abnormalities linked to the diseases (e.g., Dutta et al., 2014; Hanford et al., 2016; Northoff, 2016). Moreover, irregularities are not only observed during cognitive tasks, when subjects are engaged in a sensory, cognitive or emotional task, but also during rest, when subjects are asked to lay still in the scanner, and let their mind wander. The trend in the field of neuroimaging, towards the study of this so-called resting-state, has strongly contributed to unveiling intrinsic properties of brain disorders (Broyd et al., 2009; Greicius, 2008; Fox and Greicius, 2010; Raichle et al., 2001). Yet many questions about the neurophysiological bases of resting-state alterations remain unanswered.

A parallel stream of research explores the physical connections between brain regions by assessing structural connectivity with magnetic resonance imaging (MRI) using diffusion tensor imaging (DTI) and fractional anisotropy. These techniques allow the examination of white matter integrity and fiber tract organization and are able thereby to reveal anatomical disruptions of long-range structural connections (White et al., 2013). However, DTI is principally useful for pathologies for which we know of pre-existing structural anomalies, and less so for illnesses without obvious disruptions in connectivity (Broyd et al., 2009; Friston, 2011). Furthermore, while fMRI is promising for the investigation of the spatial organization of the cortex, it is limited by its temporal resolution and by the fact that it is an indirect measure of neural activity. Moreover, because it measures the brain's haemodynamic responses, fMRI is useful to study slow activity fluctuations (i.e. < 0.1 Hz), but is unable to capture brain activity patterns at higher frequencies. Consequently, neuroimaging methodological developments and studies of the past 10 years have been reflective of the scientific community's appreciation of the importance of electrophysiology for our understanding of network connectivity (Varela et al., 2001; Luo et al., 2010). This change is

portrayed by the flux in research employing electroencephalography (EEG), intracranical electroencephalography (iEEG), and magnetoencephalography (MEG), three tools with excellent temporal resolution. Specifically, a spotlight has been shined on the behavior of local and long-range synchronized brain oscillations in healthy cognition and, also, as potential markers for altered neural connectivity in (psychiatric) diseases (Hasey and Kiang, 2013; Başar et al., 2015; Siekmeier and Stufflebeam, 2010; Jesulola et al., 2015).

When small neighbouring neuronal populations synchronize their oscillations, local assemblies are forged, and coupling among these small assemblies can bridge distant areas (creating long-range connections) (Varela et al., 2001). Disruptions in this mechanism could unravel a number of neuro- and psychopathologies. Neuronal synchronizations are thought to operate on short time scales, and changes in spectral power are optimally detectable by electrophysiological recordings. Thus, we can examine neural network connectivity patterns by measuring the electrophysiological activity of two or more brain regions of interest using EEG, iEEG or MEG (Robinson and Mandell, 2015). Of increasing interest, MEG (Cohen, 1972) has emerged as a valuable, non-invasive, tool to assess local and long-range modulations of synchronized neural activity in human subjects (e.g. Gross et al., 2013; Jerbi et al., 2007; Hamalainen et al., 1993; Hamandi et al., 2016; Pang and Snead III, 2016; Siekmeier and Stufflebeam, 2010; Stam, 2010; Wilson et al., 2016).

Although EEG permits the probing of large scale networks, with high temporal resolution, MEG has a number of advantages. For instance, the magnetic signal that is captured by MEG is less distorted by brain tissue and skull than the electrical field detected by EEG. Additionally, MEG source-reconstruction methods can provide valuable spatial information to better characterise neural network modulations. Finally, in the context of clinical research, and more specifically in psychiatry, the fast and easy set-up of the MEG system is likely to be less unnerving for patients than the lengthy procedure of EEG. Taken together, exploration of the potential of MEG in psychiatry is an important endeavor that could lead to better understanding of psychopathology. Further details about the technical aspects of MEG have been overviewed elsewhere (e.g. Stam, 2010; Uhlhaas et al., 2017; Gross et al., 2013; Hamalainen et al., 1993).

2.2.1.2 Purpose of this review

Despite being the object of a thriving field of clinical research, the investigation of intrinsic neural network alterations in psychiatric illnesses is in its early days and is predominantly conducted using fMRI or EEG. The recent contributions and future promise of MEG in this field are not fully recognized and valued. In the present paper, we review recent findings in MEG resting-state connectivity within two mood disorders: major depressive disorder (MDD) and bipolar disorder (BD). Most importantly, this review provides a critical assessment of currently employed methods and outlines important limitations that need to be considered in future resting-state MEG studies of mood disorders.

2.2.1.3 Important concepts and terminology

Resting-state networks: When subjects are asked to lay or sit still in an MRI, PET, EEG or MEG set-up, and to let their minds wander, the activity that arises is one that speaks of the fundamental organization – or disorganization – of the brain (e.g., Brookes et al., 2011; Buckner et al., 2008; Deco et al., 2011; Shehzad et al., 2009). Resting states can be categorized into several networks (on the order of 7 ± 1): the sensori-motor network, the primary and extra-striate visual network, the auditory network, lateralized fronto-parietal networks, the temporo-parietal network, the central executive network (CEN) and the, most extensively studied, Default Mode Network (DMN), (Beckmann et al., 2005; Van Den Heuvel et al., 2009; J S Damoiseaux et al., 2006; Biswal et al., 1995; Buckner et al., 2008; Mulders et al., 2015; Fox and Raichle, 2007). The DMN englobes primarily the medial prefrontal cortex (mPFC), the posterior cingulate cortex and the precuneus cortex, as well as the inferior parietal cortex, the lateral temporal cortex and the subgenual anterior cingulate cortex (Buckner et al., 2008; Mulders et al., 2015). A large amount of evidence shows the DMN to be deactivated when one is engaged in a cognitive or sensorimotor task, and active during rest or meditative tasks (Öngür et al., 2010; Raichle et al., 2001; Allen et al., 2014; van den Heuvel and Hulshoff Pol, 2010). Of particular interest, disruptions in this network have been linked to the occurrence of psychopathological symptoms (e.g., depressive, manic, or psychotic episodes) (Mulders et al., 2015; Buckner et al., 2008; Buckner, 2013; Karbasforoushan and Woodwardm, 2012; Vargas et al., 2013).

Anatomical, functional and effective connectivity: The literature on neural network connectivity, particularly graph theory, suggests that the purpose of a node is guided by how it is connected to

other nodes in a given network, and that its function is a consequence of the action of its integral network (Buzsáki and Draguhn, 2004). Hence, when resting-state activity is observed for a few minutes, the spontaneous oscillatory behaviors form consistent and reliable functional networks (e.g. Bullmore and Sporns, 2009). The efficiency of the connections within and between these networks appears to rely on at least two main factors: epigenetics and experience (Friston, 1998). The first factor pertains to the interaction between genes and the growth of brain structures, while the second pertains to intrinsic neural activity and activity-dependent changes in synaptic strength (e.g., learning) elicited by a person's interaction with their environment.

Three types of connectivity are generally examined: anatomical, functional and effective. First, anatomical connectivity pertains to the physical connection between brain regions. It is typically examined using MRI-based DTI analysis of white matter, axonal, tracts (Rubinov and Sporns, 2010). Second, functional connectivity is used to describe the statistical dependency of time-series' activity arising from two brain areas (Hillebrand et al., 2012; Friston, 2011; Schoffelen and Gross, 2009). It can be measured using linear and non-linear tools such as correlations, coherence, phase-lag index and mutual information (Wang et al., 2014; Knösche and Tittgemeyer, 2011; Sakkalis, 2011; Stam et al., 2007). It is important to note that, while evidence from both human and animal work shows a close relationship between structural and functional connectivity (Greicius, 2008; Honey et al., 2007; Damoiseaux and Greicius, 2009; Greicius et al., 2009), direct anatomical linkage is not necessary for functional connections to take place (Honey et al., 2009; Damoiseaux and Greicius, 2009). Finally, effective connectivity speaks of the direct or indirect influence of one brain system on another based on neuronal coupling (Friston, 2011; Bullmore and Sporns, 2009), and can be measured using metrics such as Granger causality and direct transfer functions (Astolfi et al., 2004). In this review, we focus on functional connectivity abnormalities across major depressive disorder and bipolar disorder.

Local power modulations vs long-range inter-areal connectivity in MEG and EEG: It has been proposed that local and long-range neural synchrony patterns speak of the inherent organization of the brain (Mathalon and Sohal, 2015; Buzsáki and Draguhn, 2004) and, thus, an exploration of oscillatory rhythms could help us understand the fundamental neural functioning of different populations. However, confusion can emerge for investigators that are new to the discussion on neural network connectivity. This confusion is entangled in the lack of consistency in the

vocabulary employed to describe the two different processes of local and long-range synchrony. It has been argued that when neural populations synchronize, it is a phenomenon that expands across multiple temporal and spatial scales, from local integration of information within areas that specialize in the same functions to long-range connections that connect different modalities of an object (Varela et al., 2001). Generally speaking, *local synchrony* is what is captured by power estimation from a single brain signal (e.g. data from one channel or cortical source). By contrast, *long-distance synchrony* is captured by estimating the coupling between data from two brain signals.

Specifically, **local power modulations** of a neural population reflect the activity of a small spatial area of neurons on the order of 1 cm (based on experiments in visual networks; e.g. Girard et al., 2001). The measure of spectral power is taken as a reflection of the amplitude of oscillations at different frequencies (Uhlhaas and Singer, 2013). Neurophysiological studies have underlined the importance of examining local synchronization in order to observe the different types of information that are carried by different frequency bands (Varela et al., 2001; Uhlhaas et al., 2008). As for **long-range connectivity**, it reflects the functional coordination and synchronization of time-series from two brain regions that may or may not have direct structural linkage (e.g., through myelinated white matter tracts). This type of connectivity bridges brain areas between and within different neural networks (Mathalon and Sohal, 2015; Buzsáki and Draguhn, 2004; Spellman and Gordon, 2015; Uhlhaas and Singer, 2013).

While local and long-range synchrony can both be measured at sensor and source levels during EEG and MEG studies, caution should be taken when measuring the statistical or coherence differences between two recording (sensor) sites. Indeed, what may first be thought to be coordinated time-series reflecting connectivity between two brain areas (Buzsáki and Watson, 2012), may in fact be spurious coupling arising from volume conduction or field spread (e.g. Marzetti et al., 2008; Schoffelen and Gross, 2009). Different methods have been proposed to overcome this challenge. A solution that can be applied to reduce the impact of this linear mixing limitation is to use coupling measures that are not overly affected by field spread and perform the connectivity estimations in MEG source space (cf. Nolte et al., 2004; Stam et al., 2007; Schoffelen and Gross, 2009; Vinck et al,. 2011) (see section 2.2.4.4).

2.2.2 Abnormal connectivity in psychiatric disorders: where do we stand?

The following section provides a brief and non-exhaustive multi-modal overview of the rapidly increasing body of neuroimaging research that links psychiatric disorders to pathological alterations in neuronal connectivity, in line with previous work that overviewed network connectivity in SZ (Uhlhaas, 2013; Uhlhaas and Singer, 2013) and depressed patients (Mulders et al., 2015) across different neuroimaging modalities. Because of the current effervescent nature of this field, an in-depth account of the neuronal network dysfunction in mental illness is beyond the scope of this review. Instead, we will focus on findings that are particularly relevant to past, current, and potentially future resting-state magnetoencephalographic investigations. With this in mind, we first describe recent resting-state EEG and fMRI evidence that suggests dysfunctional intrinsic neural communication in major depressive (MDD) and bipolar disorders (BD).

2.2.2.1 Major depressive disorder (MDD)

With over 100,000 scientific papers on PubMed, depression is the most common and the most studied psychiatric illness in humans. MDD is characterized by features such as low mood and/or a loss of interest in daily activities for an extended amount of time and, typically, involves ruminative, self-referential thoughts (American Psychiatric Association, 2013b). A lifetime prevalence of 11.3 % has been reported in Canada (Satistics Canada, 2012) and 16.2% in the US (Kessler et al., 2003), while across the world, it is estimated that 350 million individuals suffer from depression (World Health Organization, 2016). While a number of impactful task-based studies have explored alterations in oscillatory synchronizations (e.g., Anand et al., 2005a; Silbersweig, 2013; Vasic et al., 2009), the following subsections will focus on resting-state fMRI and EEG studies in MDD population.

2.2.2.1.1 FMRI resting-state connectivity findings in MDD

Given the DMN's role in self-referential behaviors (Raichle, 2001; Buckner, 2008), this network, particularly the medial prefrontal cortex (medial PFC), is recurrently noted as a region important for the discrimination of depression from normal population (Iwabuchi et al., 2015; Kaiser et al., 2015; Mulders et al., 2015; Gong and He, 2015). Specifically, fMRI studies show depressed patients to display increased connectivity between certain nodes of the DMN (for instance,

between the subgenual anterior cingulate cortex (ACC) and the posterior cingulate cortex (Berman et al., 2011)) that could be detrimental to cognitive processes (Broyd et al., 2009; Greicius et al., 2007). These findings are supported by reviews that also highlight enhanced patterns of connectivity within these areas of the DMN (Whitfield-Gabrieli and Ford, 2012; Northoff, 2016). In addition, studies have observed altered connectivity between nodes of the DMN and the nodes of the CEN. For instance, one study found enhanced connectivity between the dorsolateral PFC and the subgenual ACC (Fox et al., 2012), while a review found decreased connectivity between the inferior/superior parietal DMN & dorsal CEN (Northoff, 2016).

Moreover, a number of original studies and reviews have reported atypical functional connectivity within areas key to emotional processing. Indeed, limbic regions (amygdala, insula Veer et al., 2010; Zeng et al., 2012), parts of the DMN (medial PFC, Gong and He, 2015; Zeng et al., 2012), and long-range connections between the DMN and the limbic system (e.g., thalamus and posterior cingulate cortex, Greicius et al., 2007), as well the CEN and the limbic system (e.g., dorsolateral PFC and amygdala, Dannlowski et al., 2009; He et al., 2016; Siegle et al., 2007) appear reduced in patients compared to controls. However, connectivity between the saliency network (i.e. anterior insula, dorsal anterior cingulate cortex) and the anterior DMN (Mulders et al., 2015), as well as between the insula and the amygdala (Avery et al., 2014) seems enhanced in depressed individuals when compared to controls.

All in all, within and between network connectivity of the DMN and limbic system appear to be altered in MDD patients, particularly with respect to projections involving the subgenual ACC. The atypical resting-state organization of their brain appears to correlate with their cognitive and emotional symptoms (Drevets, 2007).

2.2.2.1.2 EEG resting-state connectivity findings in MDD

2.2.2.1.2.1 EEG power modulations (local synchronization)

Examinations of local synchronizations in depressed populations have consistently found low-frequency bands (< 20 Hz) to display enhanced power and coherence across most brain regions (Koo et al., 2015; Leuchter et al., 2015, 2012; Northoff, 2016; Olbrich et al., 2014; Schulman et al., 2011). However, power modulations in higher frequency band (> 30hz) do not seem to be a

discriminative factor to differentiate the resting-state of depressed and control subjects (e.g., Northoff, 2016).

2.2.2.1.2.2 EEG connectivity (long-range synchronization)

Similar to findings from fMRI, EEG studies have found disruptions and asymmetrical connectivity patterns within the frontal lobe of MDD patients in theta (5-7 Hz) and alpha (8-13 Hz) frequency bands compared to healthy control subjects (Fingelkurts et al., 2007; Keeser et al., 2013). Treatment-based EEG studies established once more the importance of the subgenual ACC. Indeed, depressed patients appear to show enhanced connectivity within nodes of the DMN, and between nodes of the DMN and the CEN (Olbrich et al., 2014; Northoff, 2016). Specifically, enhanced connectivity in alpha-band (8-12 Hz) between the subgenual ACC and left medial PFC is observed before antidepressant treatment, which switched into enhanced connectivity in beta-band (12.5-20 Hz) between the subgenual ACC and right medial PFC after antidepressant treatment, thus underlying the recurrent asymmetrical connectivity patterns observed in MDD patients' frontal lobe (Olbrich et al., 2014; Keeser et al., 2013). Moreover, it has been suggested that alterations in fronto-temporal connectivity in delta/theta (1-8 Hz) frequency range could be used a marker to predict responders and non-responders to antidepressant medication (i.e. selective serotonin reuptake inhibitor), with hyperconnectivity between these areas being associated to poorer response (Lee et al., 2011).

The observations discussed above are consistent with insights achieved using deep brain stimulation (DBS) in MDD patients. Clinical trials with deep brain stimulation (DBS) have targeted the overactive subgenual anterior cingulate cortex (subgenual ACC) and the thalamocortical pathway, for the treatment of severe depression (Mayberg et al., 2005; Johansen-Berg et al., 2008). While the success of such surgical procedure is still debated (Lozano et al., 2012; Kennedy et al., 2009, 2011; Puigdemont et al., 2012; Morishita et al., 2014;), DBS involves the implantation of intracranial electrodes that allow a rare window into the circuitry of MDD.

2.2.2.2 Bipolar disorder (BD)

Bipolar disorder (BD) is a functionally debilitating disorder. The main categories of BD are BD-I and BD-II, which are characterized by either a combination of manic episodes and depression, or

by hypomania episode(s) and depressive symptoms, respectively (American Psychiatric Association, 2013b). A lifetime prevalence of 2.6 % has been reported in Canada (Satistics Canada, 2012) and around 4% (across all types of BD) in the US (Merikangas et al., 2007), while across the world, it is estimated that 60 million individuals suffer from BD (World Health Organization, 2016).

Task-based fMRI/EEG studies that have explored connectivity patterns in BD population have found synchronization alterations that differentiates them from healthy individuals (Almeida et al., 2009; Versace et al., 2010; Wang et al., 2009). However, in this section, we will explore the research that have studied BD patients during a resting-state condition.

2.2.2.2.1 FMRI resting-state connectivity findings in BD

Multiple fMRI studies have attempted to untangle the connectivity anomalies observed in these patients, with somewhat contradicting results. Indeed, depending on the analytical method used to extract connectivity, whether it be independent component analysis (ICA) or seed-based/regions of interests (ROIs), wavering conclusions have been made on BD patients' cortico-limbic connectivity patterns (e.g. Chase and Phillips, 2016).

While DMN activity has been closely linked to mind wandering and interoceptive thoughts (Raichle et al., 2001; Buckner, 2013), it has also been shown to be germane to social cognition, which is known to be impaired in psychiatric disorders (Piguet et al., 2015; Magioncalda et al., 2015; Reinke et al., 2013). A number of fMRI studies have summarized that most bipolar patients and their unaffected relatives have decreased connectivity within the nodes of the DMN (Öngür et al., 2010; Martino et al., 2016), between the medial PFC and the insula compared to controls (Calhoun et al., 2012). Hyperconnectivity has been noted between the DMN and the CEN (Chai et al., 2011), the DMN and the temporo-parietal network (Öngür et al., 2010), and the DMN and the visual and the auditory networks (Öngür et al., 2010; Rashid et al., 2014) compared to controls. Finally, the predominant result of this research in BD, based on reviews of fMRI and DTI studies, shows altered connectivity between parts of the DMN (e.g., medial PFC) and the limbic system (e.g., amygdala, Chai et al., 2011; Chase and Phillips, 2016; He et al., 2016; Houenou et al., 2012; Phillips and Swartz, 2014; Strakowski et al., 2012; Vargas et al., 2013).

With respect to the ventrolateral PFC, contradicting findings have been reported, with some estimating enhanced connectivity with the amygdala (Strakowski et al., 2012; Chase and Phillips, 2016), while others diminished (Liu et al., 2014) compared to controls. In addition, a number of studies have investigated the influence of psychotic symptoms on network connectivity patterns during resting-state. For instance, one paper observed hypoconnectivity within the PFC, and between the dorsolateral PFC (CEN) and amygdala (Anticevic et al., 2013), that was predominantly present in BD patients who presented with a history of psychosis, and not in non-psychotic BD or controls.

All in all, models proposed by many researchers suggest that disruption between these keys areas, particularly connectivity involving the amygdala, underlie the occurrence of manic symptoms and inefficient emotional management (Strakowski et al., 2012; Chase and Phillips, 2016).

2.2.2.2.2 EEG resting-state findings in BD

2.2.2.2.2.1 EEG power modulations (local synchronization)

EEG analyses of local synchronization have predominately reported group differences in the frontal region and the cingulate cortex. Examinations in modulations of local oscillatory behavior in the frontal cortex show enhanced power in alpha 8-13 Hz (Nusslock et al., 2012), beta and gamma (Howells et al., 2012; Kam et al., 2013) frequency bands compared to controls. In the cingulate cortex, low-frequencies, theta and alpha, had decreased power (Howells et al., 2012; Kim et al., 2013; Yener and Başar, 2013), while higher frequency bands, beta (15-30 Hz) and gamma (30-50 Hz), displayed increased power compared to controls (Howells et al., 2012; Kam et al., 2013).

2.2.2.2.2.2 EEG connectivity (long-range synchronization)

With respect to long-range connectivity, an EEG investigation noted decreased connectivity in the alpha (8-12 Hz) frequency band within fronto-central and centro-parietal neural network connections of patients compared to healthy controls (Kim et al., 2013). However, more studies are needed to confirm this finding and increase the specificity of the affected regions. The accumulated evidence from multi-scale modalities (e.g., fMRI and EEG) indicates that individuals

affected by BD display atypical local and long-range connectivity patterns within the nodes of the DMN and between the PFC and the amygdala.

Taken together, the fMRI and EEG findings in MDD and BD patients indicate that these populations may have difficulties processing and transferring information economically that can be detectable as connectivity anomalies between and within resting-state networks. Research into pathological alterations of resting-state activity provides critical insights into large-scale network dynamics which complement key findings that continue to emerge from task-based studies (Perry and Singh, 2014). In the next section, we will overview the results of MEG studies that examined resting-state connectivity and alterations in frequency-band modulations within the MDD and BD. We will also examine the overlap in connectivity findings that has been reported across different resting-state neuroimaging modalities.

2.2.3 Resting-state MEG connectivity and mood disorders: What do we know?

Although still in its early days, MEG has led to important clinical insights in numerous brain disorders and has become a promising tool for clinical and translational research in psychiatry (Williams and Sachdev, 2010; Siekmeier and Stufflebeam, 2010). In the following, we will focus specifically on MEG contributions to elucidate resting-state alterations in mood disorders.

2.2.3.1 Major depressive disorder

A hierarchical approach was taken in order to isolate the key-words that were most appropriate for this review. First, we began with "MEG + condition ", where condition was the general term for either MDD (i.e., depression), and BD (i.e., bipolar). We then refined this search by adding the term "resting" in order to capture studies that included a resting-state paradigm. Finally, we used the term "connectivity", in order to capture publications that also evaluated long-range synchronization, as resting-state alone, could potentially refer to power analyses. Various combination of these terms, as well as cross-referencing, was employed to ensure that all studies investigating MEG resting-state local power and long-range synchrony in MDD and BD patients were considered.

Here, a PubMed search using the key words "MEG + connectivity + depression" resulted in 16 hits, 12 of which were however unrelated to our topic of interest. Another search of the key words "MEG + depression + resting" yielded 12 studies, with only 2 studies being relevant additions to this review. Among the articles that were found, the final count of scientific articles included in this paper is of 5.

2.2.3.1.1 Altered resting-state MEG power patterns in MDD

The recent article by Jiang et al (2016) compared the oscillatory activity of major depressive disorder (MDD) patients to those of age- and education-matched control subjects. Depression correlated with power decrease in theta (4-8 Hz) and alpha (8-14 Hz) frequency bands in the frontal and parietal areas, respectively, as well as with enhanced power in beta-band (14-30 Hz) oscillations in the DMN. Similar to EEG findings, no significant difference was found between the two populations across higher frequency bands (>30 Hz, Jiang et al., 2016).

Moreover, Li and colleagues (2013) examined MEG signals in treatment-resistant MDD individuals who received 10 daily repetitive transcranial magnetic stimulation (rTMS) in the region of the dorsolateral PFC for 2 consecutive weeks. The authors normalized the spectral amplitude of five frequency bands (delta, 2–4 Hz; theta, 4–8 Hz; alpha, 8-13 Hz; beta, 13–30 Hz; and gamma, 30–50 Hz) by the mean power across all bands to obtain a relative amplitude index for each oscillatory band. Moreover, they measured frontal alpha asymmetry (FAA) in all their subjects, as FAA had been previously associated with symptom severity in depression (Zotev et al., 2016). This paper however found no significant difference between patient and control subjects in terms of FAA, similar to the inconclusive results of previous electrophysiological studies on FAA e.g.: (Brzezicka et al., 2016; Jesulola et al., 2015).

2.2.3.1.2 Altered resting-state MEG connectivity patterns in MDD

Table 3 summarizes the details of the four studies on MEG resting-state connectivity in MDD patients. The article by Nugent and colleagues (2015) demonstrated that resting state networks are altered in MDD patients compared to controls in beta-band (14-30 Hz). Specifically, based on temporal ICA analyses and correlations in source-space, they found patients to have altered connectivity between nodes of the DMN and the limbic system. Specifically, long-range connectivity between the subgenual anterior cingulate cortex and the hippocampus was diminished

in patients (Nugent et al., 2015). Moreover, the authors observed MDD patients to show enhanced connectivity between the right insular-temporal region and parts of the limbic system (i.e., amygdala, thalamus), and the left insular-temporal region and the angular gyrus in the parietal lobe and the precentral gyrus, which is part of the posterior region of the frontal lobe (Nugent et al., 2015).

In a follow-up MEG study (Nugent et al., 2016), the same authors sought out to examine the effect of ketamine on long-range synchronizations in MDD patients. The source-space connectivity patterns that were uncovered were similar to the disrupted areas found in their earlier paper (Nugent et al., 2015). In the beta frequency band (14-30 Hz), 0.5 mg/kg of ketamine restored the abnormal hyper-connection between amygdala and insula-temporal regions to normal levels. Interestingly, the authors noted that ketamine appeared to decrease all connectivity patterns across all the regions of the brain, regardless of the subjects' baseline activity.

Pathak and colleagues (2016) recently used the magnitude-squared coherence to estimate long-range connectivity in depressed individuals before and after rTMS in the dorsolateral PFC at 10Hz. Their source-space findings (via minimum norm estimate) reveal that symptom improvement after four weeks of treatment correlated with changes in the connectivity within the DMN. Post-TMS, MDD patients found increased coherence between the dorsolateral PFC and the amygdala and the pregenual cingulate cortex in the delta-band, as well as decreased coherence in the gamma band between the dorsolateral PFC and the subgenual ACC before treatment (Pathak et al., 2016). The findings of this paper could imply that baseline connectivity patterns in MDD involve diminished coherence between dorsolateral PFC-amygdala and dorsolateral PFC-pregenual cingulate cortex, along with enhanced coherence between dorsolateral PFC-subgenual ACC. Moreover, the outcome of this study underlines the importance of analyzing and reporting the type of treatment received by patients as it directly affects neural network organization.

Finally, Li and colleagues' longitudinal study (2013) explored connectivity in alpha-band oscillations in the prefrontal cortex (via MEG) and glucose-metabolism in the thalamus (via PET), which is typically underactive in MDD patients. For the analysis of PFC and thalamus connectivity, patients were divided into binary categories of responders and non-responders to 2-week treatment of rTMS at 10 Hz. Patients were categorized based on their symptom ratings on

the Hamilton Depression Rating Scale in the 8th week of the study. This type of antidepressant treatment was able to rescue the disrupted functional connection in responders 14 weeks after the start of the study, while this did not succeed in non-responders. Thus, according to the authors, their sensor-space finding could be seen as additional evidence that the strength of prefronto-thalamic connectivity could be an index of depressive symptoms, as previously observed in fMRI studies (Greicius et al., 2007).

The main finding of these MEG papers speak of altered long-range connectivity between the DMN and the CEN. Particular, the resting-state MEG literature supports previous fMRI studies that have demonstrated the implication of the subgenual cingulate cortex, the dorsolateral PFC and the thalamus in illness severity and symptomatology in MDD (e.g. Greicius et al., 2007). Importantly, this brain region is typically targeted for deep brain stimulation and rTMS in treatment resistant depressed individuals, and is thus critical to the understanding of their resting neural networks (Drevets et al., 2008; Jaworska et al., 2016; Johansen-Berg et al., 2008; Mayberg et al., 2005).

2.2.3.1.3 Relationship to task-based MEG findings

This section explores task-based MEG studies that corroborate connectivity results from resting-state MEG studies in MDD.

A number of studies have investigated the long-range connectivity patterns that emerge during affective and cognitive tasks in psychiatric patients. Amongst their findings, the diminished long-range synchronization between the dorsolateral PFC and the amygdala, observed recently in resting-state MEG by Pathak et al (2016), was also observed by Lu et al (2012). Indeed, the authors explored effective connectivity within the prefrontal-limbic system circuit using dynamic causal modeling analysis (Lu et al., 2012). During the affective task, subjects viewed 3-second clip of faces that were eating, neutral, happy or sad, and then indicated by button-press if the expression was sad or not. Under the most optimal model, patients had decreased connectivity from the dorsolateral PFC to the amygdala compared to controls. The authors hypothesized that this could explain part of the dysfunction observed in MDD patients with respect to the integration of both affective and cognitive information for overt behavior.

Other connectivity alteration in MDD patients have also been noted in task-based MEG studies. Specifically, a measure of wavelet coherence has shown enhanced connectivity between the anterior cingulate cortex (ACC) and the amygdala in the gamma (30-48 Hz) and in the delta (below 4Hz) frequency bands (Lu et al., 2013 a). Moreover, enhanced connectivity between the amygdala and the inferior frontal gyrus, as well as between the amygdala and the anterior cingulate cortex, in patients, were found to be highly discriminative features during the aforementioned affective task to differentiate MDD and control subjects (Lu et al., 2013 b). These connectivity alterations have yet to be observed in resting-state MEG findings. It may be the case that these differences in long-range synchronizations are due to the nature of the task or, rather, that they are best detected by these emotion-based paradigms.

Lastly, Salvadore et al (2010) used the widespread working-memory task, N-back, to investigate how the connectivity patterns of MDD patients change before and after a single ketamine infusion. During this task, subjects were asked to keep in mind a stimulus (number between 1 and 4) and to respond when it was matched to the observed stimulus either right away, or one or two trials previously. Using source-coherence analysis, the authors observed that the connectivity strength between the pregenual ACC and the left amygdala correlated negatively with the effect of treatment. Indeed, stronger coherence between these two regions prior to ketamine infusion correlated with improvement in symptoms. Similar findings about altered long-range synchronization between the subgenual ACC and the amygdala have been observed in intracranial EEG/DBS studies (Mayberg et al., 2005; Johensan-Berg et al., 2008). Given the reoccurring report of involvement of these brain regions, future resting-state MEG studies could clarify whether this pattern of connectivity alteration pertains to the nature of the task or to the intrinsic neural organization in MDD.

2.2.3.1.4 Strengths and limitations of resting-state MEG studies in MDD population

An important limitation that connectivity studies might display is that of being conducted at sensor-level rather than source-level. While most of the reported MDD studies were conducted in source-space, the article by Li et al (2013) was in sensor-space, where only 26 gradiometers (out of a possible 306 channels) from the frontal region was used. However, the article had a major strength of employing a multimodal approach to studying connectivity (MEG, PET, TMS), which

included an anatomical T1 from MRI to obtain anatomical precisions. This allowed access to a richer set of information than what is provided using a single neuroimaging tool. Next, exploring specific frequency bands can also be a limitation. Indeed, in the article by Nugent et al (2015) only the beta-band frequency range was explored, while Li et al (2013) reported only on alpha-band oscillatory behavior. A strength of the Nugent et al (2015) is that the authors took additional quality-control steps (to verify reliability of ICA estimates), as well as tested the reliability of their results by comparing it to a second data set (un-matched groups) and importantly had un-medicated SZ subjects. By doing so, the authors allowed to examine intrinsic connectivity prior to pharmaceutical effects. Furthermore, the metric of coherence and correlations can raise questions about the spatial accuracy of the long-range synchronizations observed due to potential field spread effect. Finally, small sample size can be problematic in the interpretation of findings. In their recent study, Nugent et al (2016) explored the effect of ketamine on long-range synchronization and on symptoms scores as assessed by the Mania and Depression Rating Scale (MADRS) in a subset of patients from their previous study (Nugent et al., 2015). However, this was performed in a small number of subjects. However, non-parametric statistical tests were applied to compensate for their cohort of patients. Similarly, while Pathak et al (2016)'s study was important to evaluate the longitudinal effect of repetitive TMS on neural network connectivity, the small sample of patients (n = 5) and lack of multiple comparisons put the findings of this paper at risks of Type I error, a fact acknowledged by the authors. While it is important to evaluate promising treatments, it would be interesting to evaluate its effect on connectivity patterns in a larger cohort of patients to increase reliability.

TABLE 3: MEG RESTING-STATE CONNECTIVITY STUDIES IN MAJOR DEPRESSIVE DISORDER

Paper	Frequency range (Hz)	Methods	Patients	Controls	Main findings
(Li et al., 2013)	delta: 2-4 theta: 4-8 alpha 8–13 beta: 13–30 gamma: 30–50	• Frontal alpha asymmetry and voxel-based partial correlation to examine connectivity in prefrontal-thalamic circuit (based on PET) • Sensor-space analysis • 3min eyes-open.	• 30 MDD received rTMS, • 6 males • 17 Responders: mean age: 51.9 ±10.5 • 13 Non-responders: mean age: 50.1±6.2	• 50 controls • 14 males mean age: 49.1± 7.0	MDD appeared to have impaired prefronto-thalamic functional connections compared to controls. rTMS resolved this pattern in those who responded to treatment after 2 weeks of treatment at 10 Hz in their dorsolateral PFC.
(Nugent et al., 2015)	14-30	• Correlation • Source-space analysis • 4.17min eyes-closed.	• 33 MDD • 22 males mean age: 42.8±9.9	• 19 controls • 11 males mean age: 39.3±6.5	Patients had reduced correlations between the subgenual ACC and hippocampus in a network with primary nodes in the precentral and middle frontal gyri. Patients showed increased correlations between insulo-temporal nodes and amygdala compared to controls.
(Nugent et al., 2016)	14-30	• Correlation • Source-space • 4.17min eyes-closed.	• 13 MDD • 11 males mean age: 45.0±13.2	• 18 controls • 12 males mean age: 39.0±7.3	Patients displayed enhanced connectivity between insulo-temporal areas and amygdala that were reduced to normal levels after ketamine treatment.

(Pathak et al., 2016)	delta: 2–4 theta: 5–7 alpha: 8–12 beta: 15–29 gamma: 30–59	• Magnitude-squared coherence. • Seed: dorsolateral PFC. • Source-space • 6min eyes-closed.	• 5 MDD received • TMS, 1 non-responder	n/a	Symptom improvement by 10 Hz rTMS increased connectivity between dorsolateral PFC and amygdala, and dorsolateral PFC and pregenual ACC in delta band. rTMS decreased connectivity between dorsolateral PFC and subgenual ACC.

Table 3 - caption: Overview of MEG resting-state studies examining changes in long-range connectivity patterns in subjects with major depressive disorder. Abbreviations, MDD: major depressive disorder, rTMS: repetitive transcranial magnetic stimulation, PFC: prefrontal cortex, ACC: anterior cingulate cortex

2.2.3.2 Bipolar Disorder

A PubMed search of the key words "MEG + connectivity + bipolar" resulted in no findings. However, a search of the key words "MEG + bipolar + resting" yielded 3 studies, 1 of which was an EEG study (already discussed in section 2.2.2.1.1).

2.2.3.2.1 Altered resting-state MEG power patterns in BD

Al-Timemy and colleagues (2014) were able to successfully classify BD and control populations using MEG resting-state spectral features within the delta (1.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma frequency bands (30-40 Hz). Relative power modulations in delta and theta frequency bands in the posterior region of the brain were observed to be significantly different between patients and healthy controls (Al-Timemy et al., 2014). However, the direction in these differences were not specified. The authors of this study also explored median frequency, described as the frequency that divides the area under the curve of the power map (1.4-40 Hz) into two. Their analysis found median frequency (MF) of BD patients to range between 9.92-12.54 Hz depending on the examined brain region. Furthermore, unlike healthy control subjects that demonstrated a positive correlation between their MF and age, BD patients had a negative correlation between MF and age (Al-Timemy et al., 2014).

2.2.3.2.2 Altered resting-state MEG connectivity patterns in BD

Table 4 summarizes the details of the relevant study that have been published on BD. Chen and colleagues (2008) had an interesting, although small, pool of euthymic (no overt depressive or manic symptoms) BD-I patients that was compared to matched healthy controls. The authors focused on the frontal cortex' activity thus, oscillatory modulations in only 11 of their 306 MEG channels were reported. Their spectral analysis across pairs of channels was performed using a derivative of the Similarity Index (SI) framework used by Arnhold and colleagues (Arnhold et al., 1999). Differences between patients and controls were noted based on global similarity index of channel pairs: patients displayed an increase in the synchronization of delta-band (2–4 Hz) frequencies and a decrease in beta-band (12–24 Hz) frequencies within nodes of the frontal cortex (Chen et al., 2008). While, there is a number of MEG studies that have examined alterations of spectral power in BD during tasks (e.g., Lee et al., 2010; Rich et al., 2010), as it stands and to our

knowledge, the paper by Chen et al (2008) is so far the only resting-state MEG study that has evaluated functional connectivity in BD population.

2.2.3.2.3 Relationship to MEG task-based studies

To the best of our knowledge, no MEG task-based study has explored long-range synchronizations in BD. However, EEG resting-state studies, such as one by Kim et al (2013), have observed disrupted connections within the PFC of BD patients compared to controls. Future MEG studies, with and without tasks, could help elucidate more specific neural network patterns that are either specific to the neural organization of BD patients, or, alternatively, to altered patterns of information processing.

2.2.3.2.4 Strengths and limitations of resting-state MEG studies in BD population

Although of important value, the resting-state MEG study by Chen et al. (2008) exploring long-range synchronization had a number of limitations. For instance, while significant information can be gathered by exploring euthymic patients (i.e., with no overt depressive or manic symptoms), the pool of subjects was relatively small (n=10). Moreover, in addition to being conducted in sensor-space, the authors focused on the frontal cortex' activity, with oscillatory modulations of only 11 of their 306 MEG channels being reported. The investigation of the neural network connectivity pattern of BD using MEG is clearly still in its' early days and more studies are needed to elucidate the key connectivity patterns that define this illness.

TABLE 4: MEG RESTING-STATE CONNECTIVITY STUDIES IN BIPOLAR DISORDER

Paper	Frequency range (Hz)	Methods	Patients	Controls	Main findings
(Chen et al., 2008)	delta: 2-4 theta: 4-8 alpha:8-12 beta: 12-24	Similarity index (SI); using 11 sensors from the frontal lobe Sensor-space 2min eyes-closed	10 euthymic BD-I 5 males, mean age: 32.5 ± 10.3	10 controls: 5 males, mean age: 32.2 ± 11.6	Increased synchronization of δ frequency oscillations and decreased synchronization of β frequency oscillations in the frontal lobe in BD compared to controls.

Table 4 - caption: Overview of MEG resting-state studies examining changes in long-range connectivity patterns in subjects with Bipolar Disorder. Abbreviations, BD-I: bipolar disorder type I.

2.2.3.4 Summary of MEG findings

The present overview shows that MDD individuals have enhanced connectivity patterns within nodes of the DMN (as evidenced by resting-state fMRI and EEG studies), altered connectivity between areas of the DMN and the limbic system (particularly between subgenual ACC and hippocampus, as evidenced by fMRI and MEG), hypoactivity between regions of the CEN and the limbic system (particularly dorsolateral PFC and amygdala, as observed through fMRI and MEG), between the nodes of the DMN and the CEN (particularly hyperconnectivity between the subgenual ACC and the dorsolateral PFC, as noted using fMRI, EEG and MEG), and hyperconnectivity between the insula and the limbic system (amygdala, as noted by fMRI and MEG studies). Overall, connections projections from and to the subgenual ACC, as well as the dorsolateral PFC, appears to be critical in the treatment and expression of depressive symptoms. Figure 5 illustrates the key patterns of altered long-range connectivity in MDD patients, observed both using MEG and fMRI (and in some cases also with EEG).

Most of the work in BD arises from resting fMRI research, which has observed altered connectivity between areas of the DMN and the limbic system (notably between the medial prefrontal cortex and the amygdala), hyperconnectivity between nodes of the DMN and CEN (particularly between the medial PFC and dorsal/ventro-lateral PFC), and hyperconnectivity between the ventrolateral PFC and the amygdala. Across all three neuroimaging modalities of fMRI, EEG and MEG, altered (mainly decrease) connectivity in the PFC has been noted. This hypoactivity in the frontal lobe has been thought to be due to the presence of psychotic symptoms in a proportion of BD patients (Anticevic et al., 2013). Hence, overall, the amygdala appears to be a key region in BD. Given the scarcity of resting-state connectivity studies in the BD population, we could not illustrate by a figure the intrinsic patterns affected in this pathology. This exemplifies the important need of conducting more resting-state MEG studies to support (and further characterize) the functional findings that are observed through MRI in BD. Such electrophysiological-based results, especially if conducted in source-space, could immensely improve our understanding of the fundamental network disorganization of this pathology.

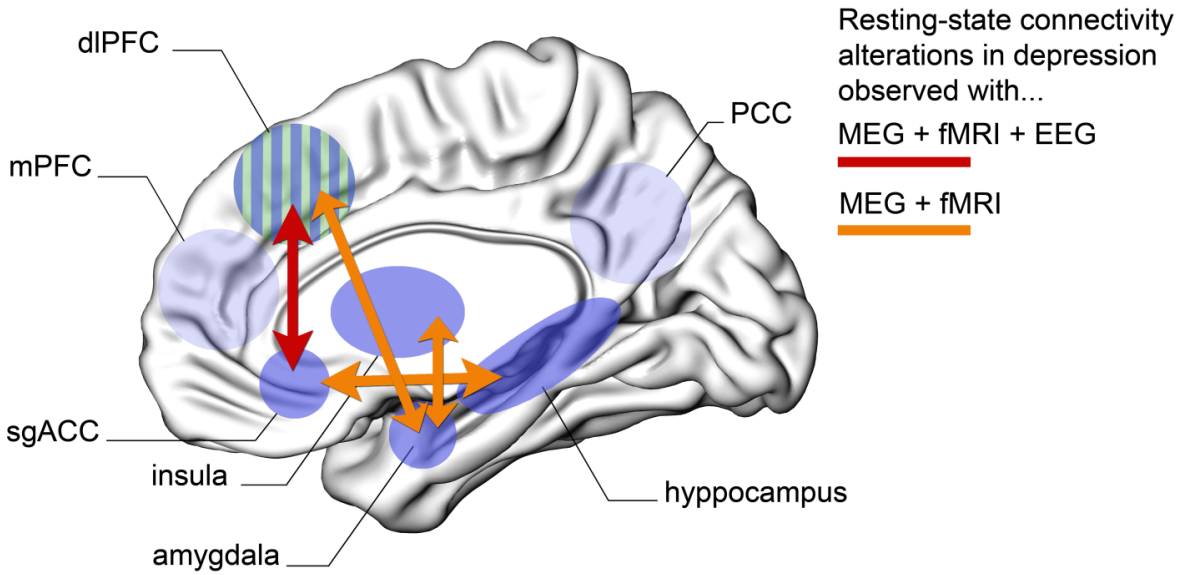


FIGURE 5: SCHEMATIC OVERVIEW OF THE KEY BRAIN REGIONS THAT SHOW ABNORMAL LONG-RANGE CONNECTIVITY PATTERNS IN SUBJECTS WITH MAJOR DEPRESSIVE DISORDER
Here, we only show areas for which evidence has been confirmed across at least MEG and fMRI modalities. Orange arrows represent altered connection between two brain regions that has been confirmed using both MEG and fMRI resting state paradigms. Red arrow represents altered resting-state connectivity between two regions that has been confirmed across MEG, EEG and fMRI. Abbreviations, MEG: magnetoencephalography, EEG: electroencephalography, fMRI: functional magnetic resonance imaging, dlPFC: dorsolateral prefrontal cortex, mPFC: medial prefrontal cortex, sgACC: subgenual anterior cingulate cortex, PCC: posterior cingulate cortex. (green-blue striped area represents dlPFC shown here from a medial view perspective for convenience).

2.2.4 Challenges, pitfalls and methodological recommendations for future studies

The assessment of resting-state connectivity patterns in psychiatric populations with MEG is a fairly new field still faced with substantial technical challenges. This section addresses the most important methodological issues that need to be understood and taken into account. Most importantly, in addition to delineating current limitations, we provide suggestions and methodological recommendations to help the field move forward.

2.2.4.1 Choosing an appropriate connectivity metric: Lack of a gold standard

In contrast to functional connectivity estimations in fMRI, where the primary measure is straightforward correlation between the BOLD time series in various voxels or ROIs, MEG connectivity estimation is a more complex endeavor (van Diessen et al., 2015). This complexity has two distinct causes: first, many common connectivity metrics come with important methodological pitfalls, and second, the richness and multi-faceted nature of neuromagnetic signals can allow the exploration of a wide variety of interactions (e.g., phase-amplitude coupling, phase-phase coupling, etc.). A question that is thus reoccurring is the following: which coupling method should one use? Choosing the right connectivity metric to assess long-range MEG coupling is a critical decision which can easily bias the results of the study.

Generally speaking, most of the commonly used interaction measures (e.g. coherence or phase-locking value) face, to various extents, limitations caused by linear mixing (source leakage), which is an inherent issue to field spread in MEG data (Schoffelen and Gross, 2009). Although several coupling measures have been proposed (e.g. Colclough et al., 2015; Hillebrand et al., 2016, 2012; O'Neill et al., 2015; Sakkalis, 2011), there is no consensus as to which one provides the best estimate of true cortical interaction. Ideally a reliable and robust measure would fulfill two criteria: it would be (a) minimally sensitive to linear mixing and (b) maximally sensitive to the specific physiological mechanisms that underlie the neural interaction. Indeed, there is not much use for a technique that is entirely immune to field spread effects if the quantity that it estimates does not capture the true physiological functional interaction. Without a clear hypothesis about the precise long-range physiological coupling mechanism, one compromise that may well be worth considering, is to examine connectivity through a combination of complementary metrics. This could be achieved, for instance, through joint exploration of phase-based and amplitude-based measures. In this context, we encourage the assessment of phase-lag index (Vinck et al., 2011; Stam et al., 2007) in parallel to band-limited envelope correlations (Hipp et al., 2012; Brookes et al., 2012; O'Neill et al., 2015).

2.2.4.2 Sensor vs Source-level analyses

While important information can be gained from combining sensor-level MEG data with advanced connectivity metrics, source-space network assessments are key to simultaneously identify the

neuroanatomical substrates and functional role of the involved networks. Moreover, source-level estimation is critical to help bridge the gap between MEG and fMRI findings in the field of psychiatry. While most of the studies reviewed here use source-space connectivity measurements (Nugent et al., 2016; Nugent et al., 2015; Pathak et al., 2016; Hinkley et al., 2011; Bowyer et al., 2015; Robinson and Mandell, 2015), most electrophysiological studies still conduct their analyses in sensor-space. A question one might ask is which source estimation technique would be considered most efficient for the specific aim of measuring resting-state MEG source-level connectivity patterns. Most of the available techniques differ in their underlying assumptions about the properties of the sources (Gross et al., 2013; Baillet et al., 1999). Attempts to infer the most appropriate source reconstruction method based on real data are hard to evaluate given that the ground truth is unknown. Using simulations can help us appreciate the strengths and limitations of a coupling method, but the extent to which it is useful for its application to real data is difficult to assess. The lack of a reliable gold standard is a concern for MEG analyses in general, and for MEG resting-state network assessments in particular. One could argue that the discussion on identifying the best inverse method might be considered an ill-posed question in itself with no unique solution. Nevertheless, we expect most families of source estimation methods (e.g. minimum-norm or spatial filters) to provide similar results when applied properly. Above all, what is most important is to understand the pitfalls and limitations of a chosen method, and their impact on source-space connectivity estimations (Hincapié et al., 2016).

2.2.4.3 Stability of MEG-based resting-state networks estimations

A challenge that is not yet entirely resolved is that of the robustness and consistency of MEG-based resting-state estimation over time and across participants. Recent research has addressed the reliability of MEG resting-state connectivity metrics (Colclough et al., 2016) and its test-retest reliability (Garcés et al., 2016). Both inter- and intra-subject consistency of MEG resting-state network estimations have been investigated and it has been found that, while variability exists, seed-based and appropriate averaging techniques allow to compare subjects between and within groups (Wens et al., 2014). Epoch length is a potential source of variability that also needs to be considered when measuring resting-state connectivity (for an EEG study, see Fraschini et al., 2016). Such parameters need to be carefully chosen prior to designing the resting-state MEG acquisition protocol. In addition, when it comes to clinical patients, it is recommended to acquire

longer resting-state data than for healthy subjects as there is a higher risk of artefacts (see next section 2.2.4.4). The psychiatry-focused studies that were reviewed here used recording lengths that varied between 2 and 6 minutes, although most of them used 3-4 minutes. A gold standard for data length in MEG resting-state protocols is lacking. Three minutes seems to be an acceptable lower limit and 4-5 minutes can be considered a reasonable recommendation, and likely necessary in the case of patient populations (where subsequent data loss is expected because of more artefacts). Similarly, there is currently no consensus on whether resting-state protocols should be performed with eyes open or closed. About half of the MEG resting-state studies reviewed here were carried out with eyes open, and the other half with eyes closed. Because of the relatively low number of resting-state studies in MEG, and because of different methodological constraints in MEG and fMRI, it seems too early to make a final decision. Given this, we would recommend acquiring both eyes open and eyes closed if possible. If this is not feasible, we suggest using eyes open with a fixation cross to minimize eye movements. Eyes closed resting-state is associated with strong alpha power increases (which might in theory interfere with subsequent network analyses), and participants are at a higher risk of getting drowsy and potentially falling asleep during the recording.

2.2.4.4 Contrasting controls and patients: Differences in artefacts and SNR

Comparisons between MEG resting-state connectivity patterns obtained in controls and patients are faced with additional difficulties caused by the pathological conditions. Increased head and body movement artefacts, eye blinks and saccades in patient populations are not uncommon, and they all lead to poorer data quality compared to data acquired in healthy subjects. For equal MEG scanning durations, artefact rejection techniques will ultimately lead to less data being preserved for the patients, which may in turn yield lower signal-to-noise ratio (SNR) in patient data compared to controls. These differences in SNR must be avoided, or at least controlled for, since they will lead to differences in functional interaction patterns that may have nothing, or little, to do with the pathology at hand, and rather reflecting differences in data quality. Minimizing data rejection through the use of artefact correction techniques such as independent component analyses (ICA) could be of interest, although the differential application of ICA to the two groups (i.e. more extensive in the case of patient data) could also lead to differences that may bias connectivity findings and data interpretation. To address artefact-related SNR discrepancies between patients

and controls, we recommend planning to acquire more data in patients from the start of the project, or alternatively to use a subsample of data from the controls to achieve comparable SNR across the two groups.

A second, often overlooked, issue is that pathological changes in local signal amplitude can affect the estimation of long-range connectivity in patients, and thereby lead to group differences that are in fact a reflection of inadequate or unreliable coupling estimation. This can occur because lower signal amplitudes (that equate noise levels) will *de facto* lead to lower SNR. A lower SNR within a given frequency band can affect, for instance, the estimation of phase. In such a case, the reduction or vanishing of a measure of inter-areal phase coupling, compared to controls, cannot be taken as an indication of connectivity break down, rather it is the result of poor phase estimation in patients due to lower local SNR. This phenomenon will also affect inter-areal cross-frequency phase-amplitude coupling. Overcoming such limitations is not trivial. A good rule of conduct is not to focus on inter-areal interaction measures alone, but to systematically calculate spectral power in the frequencies and nodes of interest. If the powers show statistically significant differences across the groups, one could attempt to randomly use subsamples of data in order to control for the effect of amplitude across the two groups (bootstrapping and stratification techniques could be useful here).

2.2.4.5 Effect of age and medication on connectivity patterns in psychiatry

In both healthy and pathological populations, age has been shown to be an important variable that can affect brain structure, cognitive functions and connectivity patterns (Fucetola et al., 2000; Tamm et al., 2002; Paus et al., 2010). At the anatomical-level, volumes of cortical grey and white matter change with age. On one hand, among neuro-typically developed individuals, grey matter density of frontal and parietal lobes displays an inverted-U pattern, with volume increasing until adolescence, then declining. However, this may not be the case of other brain regions (Paus et al., 2010; Giedd et al., 1999). On the other hand, white matter volume appears to steadily increase until around 30 years of age (Paus et al., 2010; Giedd et al., 1999). At the functional level, task-based studies in fMRI have observed focal increases in activity with age, for instance, in the dorsolateral PFC, ventrolateral PFC and premotor cortex (Kwon et al., 2002). Changes in connectivity between certain brain regions also seem to take place with age. Of note, long-range

synchronizations that underline the processes of cognitive functioning (e.g., attention, working memory, inhibition) appear to grow in strength until the third decade of life (Tamm et al., 2002; Adleman et al., 2002). Compared to these findings in healthy cohorts, deficits observed in illnesses, such as schizophrenia, are found to be similar, albeit with steeper decline in some function, such as abstract thought (e.g., Fucetola et al., 2000).

Age of illness onset is also an important factor to take into consideration as early/pre-adolescence onset of psychopathologies typically correlate with worse prognosis and more severe clinical symptoms (Clemmensen et al., 2012; Strober et al., 1988). Moreover, in BD, early onset is seen to be linked to more comorbid disorders (e.g., anxiety, substance abuse), shorter euthymic periods and more attempts of suicide (Perlis et al., 2004; Carlson, 2000). Taken together, age is a critical to factor-in when conducting connectivity analyses or correlations between symptoms and connectivity patterns, particularly in psychiatric population, to ensure that statements made about group differences are in fact due to true discrepancies between the evaluated cohorts, and not due to an age effect (Bijanki et al., 2015).

Medication is also a variable for that has substantial effects on the neural network of psychiatric patients, with different types of pharmacotherapies impacting connectivity in distinct ways (e.g., selective seratonergic vs noradregenic reuptake inhibitor, (McCabe and Mishor, 2011). A review of longitudinal MRI-based studies noted that part of the grey matter volume decreases and ventricle enlargement in schizophrenia patients could be explained by cumulative exposure to antipsychotic treatment (Fusar-Poli et al., 2013). In MDD, antidepressant treatment seems to modify the connectivity between the nodes of the DMN, as well as cortico-limbic connectivity, both at rest and during affective tasks (e.g., Gudayol-Ferré et al., 2015; Anand et al., 2005b). However, other studies find the effect of psychotropics on functional connectivity to be inconclusive (Nejad et al., 2012). Part of the difficulty in untangling the influence of treatment lies in the complexity of conducting longitudinal studies, which ideally include drug naïve patients that are either individuals at risk of developing a psychiatry illness or first-episode psychosis or mania patients, as well as chronic patients to compare to. A number of studies that have investigated birth cohorts (e.g., Jääskeläinen et al., 2015) have enlightened the field the most as they take into account

maximal information regarding context, neurodevelopmental factors, environmental influences, longitudinal notes on symptoms and treatments effects.

Finally, it is important to note that non-medication drugs, such as nicotine and caffeine, also appear to alter resting-state networks in healthy and clinical populations. Evidence of this effect have been reported using fMRI (Smucny et al., 2016; Weiland et al., 2015; Rack-Gomer et al., 2009; Zanchi et al., 2015; Jacobsen et al., 2004; Janes et al., 2012), and MEG (Tal et al., 2013). Future connectivity studies should incorporate these variables in their analyses.

2.2.5 Conclusions and future directions

This review is the first of its kind to examine the literature's findings on resting neural network connectivity patterns of bipolar disorder and major depression disorder, based on magnetoencephalography studies. A global analysis of current scientific papers demonstrates that the two illnesses display functional abnormalities that affect the way information is integrated, locally, and transferred from one brain region to another through long-range connections. Moreover, this review illustrated that resting-state neuroimaging paradigms are a useful way to access the disorganized brains of individuals with psychopathologies. Finally, although still in its early days, MEG carries the potential to significantly advance our understanding of large-scale network alterations associated with psychiatric disorders (Reite et al., 1999).

Overall, the PFC, in particular the medial PFC which is at the core of the DMN and of social cognition, is affected across both psychopathologies. Given that this brain region is one of the last to develop during neurodevelopment (Casey et al., 2000; Taylor et al., 2014), it is not surprising that most mental health issues arise during adolescence and that any early brain-damage, detrimental environmental factor, or oxidative stress can affect a person's personality, theory of mind, emotional maturity, empathy and healthy resting neural wiring (Kolb et al., 2012; Carrion and Wong, 2012; Grossmann, 2013). Of note, among depressed individuals, patterns of dysfunctional connectivity are repeatedly observed across the three major neuroimaging modalities reviewed (fMRI, EEG, MEG), particularly altered long-range connectivity between the DMN and the limbic system, as well as between the DMN and the CEN. In MDD population, the

recurrent dysfunctional connectivity patterns involved the subgenual ACC. As for the BD literature, the most consistent findings stemmed from resting fMRI studies, where functional connectivity was altered between regions of the DMN and the amygdala in BD.

An explanation for the imbalance in the amount of scientific papers published in these two mood disorders could be that depression is the mental illness affecting the largest percentage of individual world-wide in its various forms (e.g., MDD, postpartum depression, seasonal onset depression, etc.), while BD is symptomatically more complex and heterogeneous. Thus, when interpreting neuroimaging results, researchers should consider the effect of additional psychological factors, such as manic/cyclic mood and history of psychosis (Anticevic et al., 2013), as well as medication when attempting to untangle the connectivity pattern affiliated with BD.

Resting-state MEG is expected to continue gaining momentum in psychiatry. One promising application is its ability to enhance the understanding of how neuromodulation (e.g., repetitive transcranial magnetic stimulation, rTSM) can change the neural circuitry of mood disorder patients. Indeed, given the promising evidence for the use of rTMS for symptom reduction in refractory MDD patients (Salomons et al., 2014; Downar et al., 2014; Berlim et al., 2014; Tortella et al., 2015), exploring the different ways this tool changes resting-state networks after stimulation could help further elucidate connectivity patterns in these patients, and possibly lead to new neuromodulation targets for MDD.

Our recommendations for future studies are to further explore the potential of examining functional and effective neural network connectivity in psychiatric disorders using a combination of tools, multimodal imaging techniques, yet employ common terminology (Cetin et al., 2015). As far as MEG is concerned, performing the connectivity analysis in source-space is highly recommended to improve the interpretability of the findings. In addition, the informed choice of the connectivity framework and network metrics is critical to avoid misinterpretations. The use of advanced methods such as graph metrics or machine learning as a data-mining tool in this field is also a promising venue for future research. By doing so, a more complete picture of how mental illness affects information propagation can be acquired, thus allowing for the development of more efficient treatment for patients.

Chapter 3: Patient, interrupted: MEG oscillation dynamics reveal temporal dysconnectivity in schizophrenia

Abstract

Current theories of schizophrenia emphasize the role of altered information integration as the core dysfunction of this illness. While ample neuroimaging evidence for such accounts comes from investigations of spatial connectivity, understanding temporal disruptions is important to fully capture the essence of dysconnectivity in schizophrenia. Recent electrophysiology studies suggest that long-range temporal correlation (LRTC) in the amplitude dynamics of neural oscillations captures the integrity of transferred information in the healthy brain. Thus, in this study, 25 schizophrenia patients and 25 controls (8 females/group) were recorded during two five-minutes of resting-state magnetoencephalography (once with eyes-open and once with eyes-closed). We used source-level analyses to investigate temporal dysconnectivity in patients by characterizing LRTCs across cortical and sub-cortical brain regions. In addition to standard statistical assessments, we applied a machine learning framework using support vector machine to evaluate the discriminative power of LRTCs in identifying patients from healthy controls. We found that neural oscillations in schizophrenia patients were characterized by reduced signal memory and higher variability across time, as evidenced by cortical and subcortical attenuations of LRTCs in the alpha and beta frequency bands. Support vector machine significantly classified participants using LRTCs in key limbic and paralimbic brain areas, with decoding accuracy reaching 82%. Importantly, these brain regions belong to networks that are highly relevant to the symptomology of schizophrenia. These findings thus posit temporal dysconnectivity as a hallmark of altered information processing in schizophrenia, and help advance our understanding of this pathology.

3.1. Introduction

Schizophrenia is a debilitating disorder that is accompanied with severe cognitive, behavioral and functional impairments. Worldwide, ~21 million people suffer from psychotic illnesses (World Health Organization, 2016) yet, progress in understanding the pathophysiological mechanisms that underlie the symptoms of schizophrenia is relatively slow. For over 20 years, it has been suggested that dysconnectivity [*disconnection syndrome* (Weinberger et al., 1992; Friston and Frith, 1995) or *cognitive dysmetria* (Andreasen et al., 1998)], at the anatomical and functional levels, is the core dysfunction that underlines schizophrenia clinical symptoms (Friston et al., 2016).

The idea of neural dysconnectivity (i.e. the failure of functional integration in the brain) relies on the assumption that disorganization is a key characteristic of schizophrenia. According to this theory, schizophrenia is marked by patterns of symptoms involving errors in predictive coding (leading to delusions and hallucinations), lack of language and thought organization, and, in some cases, motor disorganization. Neural dysconnectivity is thought to arise from aberrant synaptic plasticity, which has been attributed in part to abnormal modulation of N-methyl-D-aspartate (NMDA) receptors by neurotransmitters such as serotonin, dopamine and acetylcholine (Stephan et al., 2009). A recent study (Shaw et al., 2019) has shown that this atypical functioning of NMDA receptors is linked to altered gamma-band oscillations in schizophrenia. Moreover, it has been proposed that these abnormal neural connections occur within (and in-between) distinct brain regions (Yeganeh-Doost et al. 2011), and thereby lead to clusters of cognitive, affective and motor symptoms.

Functional magnetic resonance imaging (fMRI) (e.g., Alderson-Day et al., 2015; Karbasforoushan and Woodward, 2012; Narr and Leaver, 2015; Ramani, 2015; Rotarska-Jagiela et al., 2010; Yu et al., 2013) and electrophysiological studies (e.g., Ioannides et al., 2004; Sponheim et al., 1994; Uhlhaas and Singer, 2010) have probed structural and functional alterations among schizophrenia patients and have found significant and consistent differences in terms of the physical properties and connectivity patterns of their neural signal compared to controls (multimodal reviews: Alamian et al., 2017; Ćurčić-Blake et al., 2016; Pettersson-Yeo et al., 2011). Among others, some of the most commonly reported differences occur within the frontal cortices, within the thalamo-

cortical pathway and between dorso-lateral prefrontal areas and amygdala (Anticevic et al., 2013; Alamian et al., 2017b). While the input from fMRI has been crucial in understanding the anatomical (spatial) disruptions and task-related changes occurring in schizophrenia, the picture remains unclear about how neural dysconnectivity occurs at the fast temporal scale of neural communication. Specifically, while details on alterations of the anatomical connections between brain areas among schizophrenia patients have been reported (e.g., Cheung et al., 2008; Wagner et al., 2015) there remains an important gap in understanding how the integrity of the neural signal is changed over time, across multi-scaled windows. This type of evidence is key for understanding whether proper information integration has taken place (Houck et al., 2016; Hirvonen et al., 2017; Henry et al., 2019).

In recent years, there has been an increasing interest in investigating the temporal dynamics of neural oscillation amplitudes (Brookes et al., 2015; Cetin et al., 2016; Sanfratello et al., 2019). An approach for quantifying the properties of rhythmic brain activity is by exploring long-range temporal correlation (LRTC) in the amplitude dynamics of different frequency bands (Linkenkaer-Hansen et al., 2001b; Nikulin et al., 2012; Palva et al., 2013a). One way to measure LRTCs is by applying Detrended Fluctuation Analysis (DFA) on either the raw electrophysiological signal, or on the envelope (i.e. amplitude) of a given frequency band, using a sliding window of a given length (Peng et al., 1995; Kantelhardt et al., 2001). The LRTC metric quantifies the self-similarity of a signal across time. Its presence is an indication that electrophysiological signal decays slowly over time, and it is thought to speak of the temporal integrity of transferred information (Linkenkaer-Hansen et al., 2001b). Interestingly, the strength of oscillatory LRTCs have been found to be highly heritable (~60%, Linkenkaer-Hansen et al. 2007) and, importantly, to be altered by disease, such as psychosis (Fernández et al., 2013).

To date, a few studies have evaluated LRTCs using DFA on resting-state EEG signal in schizophrenia. These papers showed that, while the overall temporal structure of the neural signal was maintained over time for both schizophrenia and healthy controls, it was more random in schizophrenia. Specifically, LRTCs were attenuated in the beta-band (Nikulin et al., 2012; Junfeng Sun et al., 2014; Moran et al., 2019) and alpha-band oscillatory envelopes (Nikulin et al., 2012). The present study is based on the premise that LRTCs provide an efficient marker of altered

information integration over time in schizophrenia. We propose that measuring LRTCs in cortical and subcortical brain areas, with the high temporal and spatial resolution of source-space magnetoencephalography (MEG), could provide evidence for the dysconnectivity theory of schizophrenia from a temporal point of view.

The goals of this study were to investigate how intrinsic neuromagnetic LRTCs differ among schizophrenia patients compared to healthy controls across cortical and subcortical brain areas. Moreover, we measured the relevance of these alterations in their ability to discriminate schizophrenia patients from healthy controls using a machine-learning framework. We hypothesized that the temporal properties of neural dynamics are affected by the illness and that, consequently, LRTCs as measured by DFA would be significantly diminished among schizophrenia patients compared to controls in both cortical and subcortical brain regions.

3.2 Materials and methods

Data collection was conducted at the Cardiff University Brain Research Imaging Centre (CUBRIC) in Wales, U.K., while the following analyses were conducted at the University of Montreal (Q.C., Canada). Ethics approval for the collection of data was obtained according to the guidelines of the NHS ethics Board in the U.K, the Cardiff University School of Psychology Ethics Board (EC.12.07.03.3164), and the Ethics Research Committee of the University of Montréal (CERAS-2018-19-069-D).

3.2.1 Participants

Neuroimaging and behavioural data of 26 schizophrenia patients and 28 healthy controls were collected. Control participants were neurologically and psychology healthy, and matched patients on age and gender. Patients were recruited through the Cognition and Psychosis study (i.e., from the Schizophrenia Working Group of the Psychiatric Genomics Consortium; details of the case sample recruitment and procedures are provided in (Lynham et al., 2018)), while controls were primarily recruited through ads using the Cardiff University Noticeboard and opportunistically from CUBRIC, Cardiff University. One patient was excluded due to the quality of their recording,

and three controls were excluded due to the lack of a complete set of recording conditions. The final sample size included 25 schizophrenia patients and 25 controls.

Diagnosis confirmation was obtained for patients through the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview. For both groups, participants were included in the study if they were between the ages of 16-75, had English as their first language, and normal or corrected vision. Controls were excluded if they had any history of neuropsychiatric disorders as measured by the MINI International Neuropsychiatric Interview (Sheehan et al., 1998). Participants were excluded if they had a history of drug or alcohol abuse, a diagnosis of epilepsy, head injury or stroke, metal present in their bodies or the use of mood stabilizing drugs. All participants were asked to refrain from the use of alcohol and drugs two days prior to testing.

Note that the sample size for this study was calculated taking into account the fact that we planned to use a machine learning framework. Based on the literature (i.e. multiple studies using machine learning to classify schizophrenia and controls), we expected classification decoding accuracies to roughly lie between 70 and 75%. Assuming a binomial cumulative distribution of the decoding error, and a p-value threshold of 0.001, the number of samples corresponding to a significant classification of 70 or 75% is 40 or 60 respectively (Combrisson and Jerbi, 2015). Our sample size of 50 participants fits within this interval.

3.2.2 Demographic and clinical data

Demographic information about each participant was collected, including their age, gender, depression score on the Beck Depression Inventory – II (BDI-II (Beck et al., 1996)), and mania score on the Altman Self-Rating Mania Scale (ASRM (Altman et al., 1997)). In addition, for the patient group, scores on the Scale of the Assessment of Positive Symptoms (SAPS) and the Scale of the Assessment of Negative Symptoms (SANS) (Kay et al., 1987) were derived from the psychosis-subsection of the MINI International Neuropsychiatric Interview. Finally, information on antipsychotic doses were obtained and standardized using olanzapine equivalents (Gardner et al., 2010). The data was anonymized such that no identifiable information of participants was associated with their data nor subsequent analyses. Table 5 summarizes the demographic

information of each subject group and average clinical scores on the BDI, ASRM, SANS, SAPS and medication dosage.

Aside for BDI-II scores (independent t-test, $t(46) = 4.94$, $p = 0.000011$), no significant group differences were observed. According to their scores on the BDI-II, schizophrenia patients presented on average with mild-depression, compared to controls who showed negligible signs of depression. In terms of ASRM scores, neither group showed any symptom that could correlate with mania. Finally, in terms of scores on the SANS and SAPS, patients generally appeared asymptomatic.

TABLE 5: AVERAGE DEMOGRAPHIC AND CLINICAL INFORMATION OF PARTICIPANTS

	Age	**Gender**	**Medication dose**	**BDI-II**	**ASRM**	**SANS**	**SAPS**
Controls	44.04 (±9.20)	17M; 8F	n/a	4.50(±4.67)	3.25(±3.54)	n/a	n/a
SZ Patients	44.96 (±8.55)	17M; 8F	13.03(±13.80)	14.83(±9.11)	3.46(±2.40)	3.96(±2.92)	3.72(±4.00)

Table 5 – caption: Average demographic and clinical information of participants. The ± symbol indicates the standard deviations. ASRM = Altman Self-Rating Mania Scale, BDI = Beck's depression inventory, F = females, M = males, SANS = Scale for the assessment of negative symptoms, SAPS = Scale for the assessment of positive symptoms, Schizophrenia = SZ

3.2.3 MEG and MRI experimental designs

Two five-minute resting-state MEG scans were recorded in each participant, once with eyes-closed and once with eyes-open, with a 275-channel (first-order gradiometers) CTF machine located at the CUBRIC in Wales, U.K. During the eyes-open recording, participants were instructed to fixate a red square projected in front of them. During both resting-state conditions, participants let their mind wander for the duration of the recordings. Reference channels were placed at fixed distances from the nasion, the left and right pre-auricular points. In addition, five electrodes were placed above and below the center of the left eye, under the left and the right temple and behind the left ear, to record eye movements/potential artifacts (Messaritaki et al., 2017). The raw MEG signal was recorded at a frequency sampling of 1200Hz. In addition to the MEG data acquisition, an

anatomical-T1 MRI scan was acquired for all participants to help with the MEG source reconstruction.

3.2.4 Data preprocessing and MEG source reconstruction

An in-house open-source python pipeline NeuroPycon (Meunier et al., 2020) was used for the preprocessing and source-reconstruction analysis. The continuous raw data was filtered with a zero-phase bandpass using a finite impulse response filtering (FIR 1, order =3) between 0.1 Hz and 150 Hz, and a Hamming window. The default values for lower and upper transition bandwidths and filter length were used. The data was down-sampled from 1200Hz to 600 Hz. Independent component analysis (ICA) was then used to remove blinks, eyes movements, heartbeat, and external artefacts from the MEG signal using the routine provided by the MNE-python package (Hyvarinen, 1999; Gramfort et al., 2013).

The anatomical MRI information of each participant was segmented with the FreeSurfer software package (Fischl, 2012) to generate an anatomical source-space that included both the cortical surface and the subcortical regions modelled as volumes. Given that each participant had different source-space dimensions, we next morphed and projected individual source spaces onto *fsaverage* (standardized space) of FreeSurfer (Greve et al., 2013). The mixed source space obtained in this manner consisted of 8196 nodes on the cortical surface, where each voxel was 5mm apart from one another. For subcortical structures, we applied a region-of-interest (ROI) transformation and extracted the following volumes using FreeSurfer: Amygdala, Caudate, Hippocampus, Thalamus and Cerebellum. On average, these regions contained 27, 51, 73, 130 and 875 voxels, respectively.

The lead field matrix was computed using the single layer model boundary element method implemented in MNE-python (Gramfort et al., 2013). Finally, the inverse solution was computed using the inverse pipeline provided by NeuroPycon (Meunier et al., 2020) where we chose the weighted Minimum Norm Estimate (Dale and Sereno, 1993; Hämäläinen and Ilmoniemi, 1994; Hincapié et al., 2016), implemented in the MNE-python package (Hyvarinen, 1999; Gramfort et al., 2013). The dipoles of the cortical source-space were constrained to have an orientation normal to the surface, while the dipoles of the subcortical volumes were left with free orientation. In total,

we extracted 8196 time-series at the cortical level, and 3 time-series per source in subcortical regions.

3.2.5 Measuring LRTC using DFA

To quantify LRTCs in the structure of the amplitudes of each frequency band, we used a standard procedure based on Detrended Fluctuation Analysis (DFA) (Peng et al., 1995; Kantelhardt et al., 2001), in line with previous research (Linkenkaer-Hansen et al., 2001b; Nikulin and Brismar, 2005; Nikulin et al., 2012).

Briefly, DFA measures the fluctuation of linearly detrended signal as a function of a sliding time-window. The DFA scaling exponent reflects the slope of this fluctuation function, and is often referred to as the self-similarity parameter (Lux and Marchesi, 1999). It can take on a value between 0 and 1, where a value between 0 and 0.5 represents negative temporal correlation (i.e. anti-persistence of the signal in time), 0.5 represents a random (uncorrelated) signal, and a value between 0.5 and 1 represents a positive temporal correlation (persistence of the signal in time) (Hardstone et al., 2012). Simply put, in a persistent signal, large fluctuations are likely to be followed by large fluctuations and small energy fluctuations are likely to be followed by small energy fluctuations. Conversely, in an anti-persistent signal (negative correlation) large fluctuations are likely to be followed by small fluctuations and small fluctuations are likely to be followed by large fluctuations. In other words, if the scaling (DFA) exponent decreases from a value close to 1 down to a value closer to 0.5, then the temporal correlations are considered to be less persistent in time (i.e. they decay faster in time).

In order to obtain a measure of LRTCs in the MEG signal, instantaneous amplitude of the MEG signals was computed in the delta (1-4 Hz), theta (4-7), alpha (8-13 Hz), beta (15-25 Hz), and gamma (30-60 Hz) frequency bands. To this end, the raw MEG signal was first filtered using a finite impulse response filtering (FIR1, order = 3), and then we computed the Hilbert transform (Le Van Quyen et al., 2001; Foster et al., 2016). Next, DFA values were calculated for each of the 8196 nodes of the cortex for the length of the recording as described in (Peng et al., 1995; Linkenkaer-Hansen et al., 2001b). In terms of deep structures, DFA was computed for each of the

3 time-series of each source, and then averaged across the 3 in order to obtain a single time-series per deep source. For the present study, DFA was used to analyze the decay of temporal auto-correlations, for each eyes-open and eyes-closed condition, in the time range of 5-33s (or 3000-20000 samples) over consecutive windows for the full 5 minutes of MEG recording.

3.2.6 Statistics and machine-learning analyses

3.2.6.1 Conventional statistics and correlation analyses

Group statistical analyses were conducted between schizophrenia patients and matched-controls to test for group-level differences in (a) LRTC scaling exponents (calculated on spectral amplitudes) (b) spectral amplitudes (amplitude envelope of band-passed signals), and (c) demographic and clinical data. To do so, we used non-parametric statistical tests (two-tailed, unpaired, pseudo t-tests), corrected with maximum statistics using permutations ($n = 1000$, $p < 0.001$) (Nichols and Holmes, 2001; Pantazis et al., 2005). Two-tailed, paired, t-tests were also used (within each group) to test for changes between the eyes-open and eyes-closed conditions (both for spectral amplitude and LRTC exponents). Moreover, Pearson correlation with False Discovery Rate (FDR) correction (Genovese et al., 2002) were used to explore the relationship between cortex-level LRTCs and scores on the BDI, ASRM, SANS and SAPS, as well as to investigate the link between age, gender and medication dosage and values of LRTCs. This was also repeated for correlations between amplitude and clinical scores. FDR correction (Benjamini-Hochberg) was applied to each p-value (computed for each of the 8196 nodes), and Bonferroni correction was then applied to account for all the frequency bands (5) and correlational analyses (7) to achieve a significance threshold of $p<0.05$ corrected.

3.2.6.2 Machine learning analyses

MEG signal classification was conducted using a support vector machine model and a stratified 10-fold cross-validation scheme to evaluate the discriminative power of LRTC in objectively classifying patients and controls. To do so, the DFA exponent features for each source were split into 10 folds while respecting the balance between the two classes (schizophrenia, controls). Then, the classifier was trained on the data from nine of the folds and tested on the remaining fold (test set). The classification performance was assessed using the decoding accuracy (DA) on the test set

(i.e., percentage of correctly classified participants across the total number of participants in the test set). This operation was iteratively repeated until all folds were used as test sets. The mean DA was used as the classification performance metric. In order to infer the statistical significance of the obtained DAs, permutations tests were applied to derive a statistical threshold as described in (Combrisson and Jerbi, 2015). This method consists of generating a null-distribution of DAs obtained by running multiple instances of the classification (n=1000), each time randomly shuffling class labels. Maximum statistics were applied across all sources in order to control for multiple comparisons (Nichols and Holmes, 2001; Pantazis et al., 2005). The same procedure was also applied to the comparison of spectral amplitudes between the groups. Finally, we used Visbrain for the visualizations of all cortical results (Combrisson et al., 2019).

3.2.7 Data availability

The code used throughout this study relies on open tools available to the community, including primarily the following python tools (NeuroPycon, MNE, visbrain) which can be downloaded from Github. The functions for DFA and the SVM classifiers trained in this study can be made available upon reasonable request.

3.3. Results

The following sections describe the results obtained with the eyes closed resting-state MEG protocol. The summary of the results obtained in the eyes open condition are provided in the supplementary material, and are summarized at the end of the Results section.

3.3.1 Group comparisons of LRTCs

Figure 6 shows the results of group-averaged LRTCs in cortical source-space in the schizophrenia patient group and the control group, for each frequency band. Overall, LRTCs were attenuated in patients, compared to controls, across the cortex in the theta, alpha and beta frequency bands. Interestingly, in the delta and gamma frequency bands (1st and last row of Figure 6), certain areas showed LRTCs to be enhanced in patients compared to controls. These differences were however non-significant when using conventional t-tests and corrected for multiple-comparison

($p>0.05$ for two-tailed tests). In Figure 6, the t-values reflect both the magnitude of the effect and the direction of the group differences in terms of LRTC values, with the negative (blue) t-values showing brain areas where patients have reduced LRTC values compared to controls, and the positive (red) t-values showing brain areas where patients have increased LRTC values compared to controls. By contrast, when applying a machine-learning approach to test for out-of-sample generalization in the same data, we found that LRTCs in the alpha and beta bands in multiple brain regions led to statistically significant classification of the two subject groups with up to 82% decoding accuracy (Figure 7, max statistics correction, $p<0.005$). More specifically, using source-space alpha-band LRTCs as a decoding feature led to statistically significant discrimination of schizophrenia and controls in the precentral, central and postcentral gyri and sulci, the right frontal gyrus, the left temporal gyrus, the bilateral temporal poles and sulci and the medical parts of parahippocampal gyri (Figure 7a). Meanwhile, using source-space beta-band LRTCs as a decoding feature let to statistically significant classification of schizophrenia patients and controls in the bilateral orbitofrontal cortices, the right parahippocampal gyrus, bilateral orbital gyri, bilateral anterior cingulate gyri and sulci and left insular sulcus (Figure 7b). To illustrate how the classifier was able to successfully separate patients from controls, we computed individual LRTC values, averaged in each subject across all brain sites that exhibited successful decoding. These were computed separately for alpha and beta-band LRTCs and are presented in a scatter plot (Figure 8a). For comparison, Figure 8b shows individual alpha and beta amplitude values averaged over the same brain regions. As can be seen, amplitude values in the alpha and beta bands in the same nodes do not allow for a clear separation of the groups. This provides further qualitative confirmation that the LRTC-based classification results are not driven by changes in amplitude. Figure 9 shows the classification results of schizophrenia and controls using the estimated alpha-band and beta-band LRTCs from the estimated time-series in deep structures. In terms of subcortical structures, statistically significant classification (max statistics correction, $p<0.001$) of schizophrenia versus controls was obtained with alpha-band LRTC features from the combination of the left and right amygdala, the left hippocampus, the left thalamus and the combination of the left and right cerebellum (Figure 9a). In the beta frequency band, the right amygdala, the combination of the left and right amygdala, the combination of the left and right caudate, and the combination of the left and right thalamus were able to statistically significantly (max statistics

correction, $p<0.001$) discriminate the two groups with a success rate of up to 74% (Figure 9b). No other frequency band's LRTCs led to significant classification.

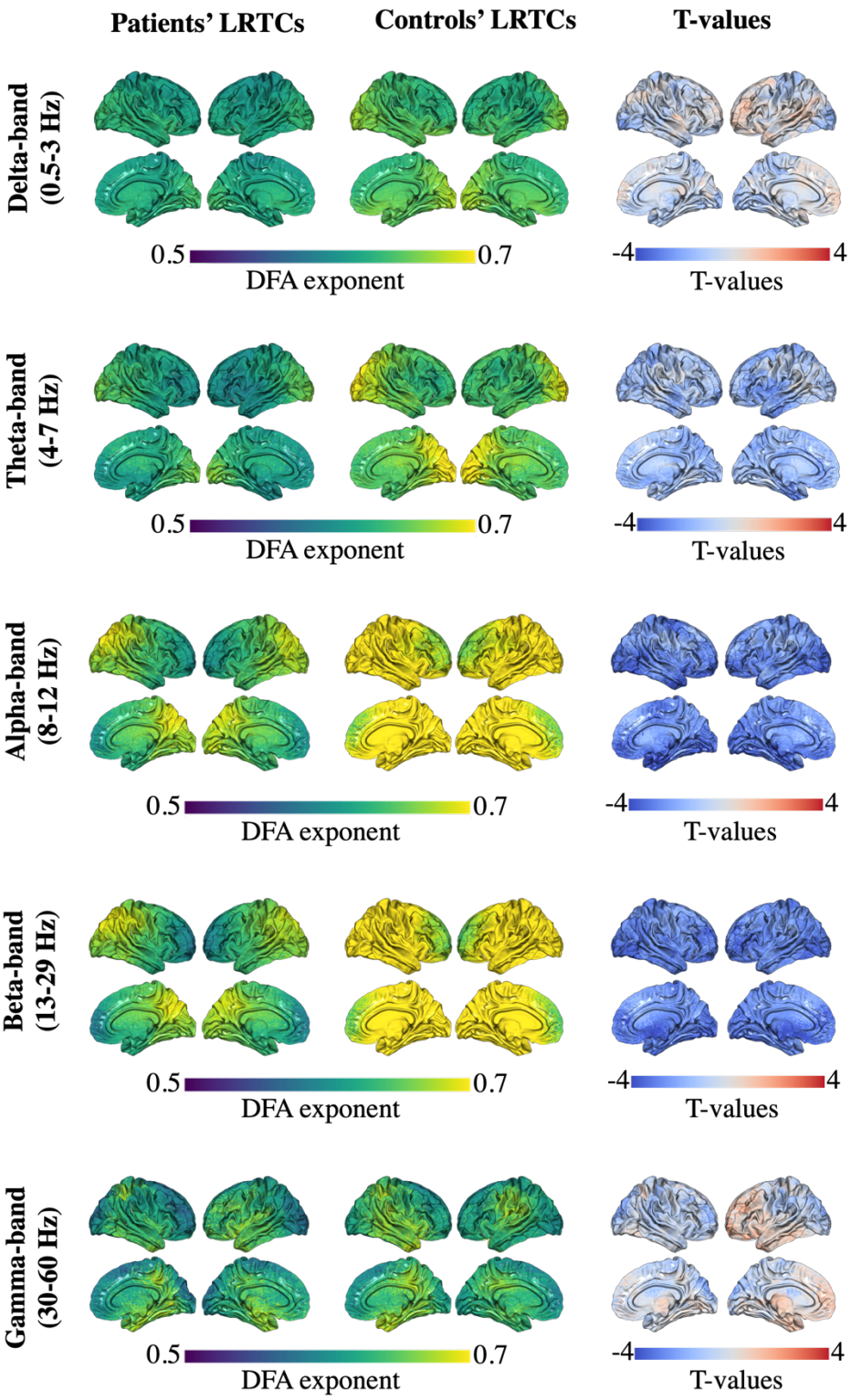


FIGURE 6: SOURCE-LEVEL RESULTS OF LRTCS OF SCHIZOPHRENIA PATIENTS AND CONTROLS
Columns 1 and 2 show mean LRTC values for each group. Column 3 shows the T-values of the unpaired t-tests (non-significant). DFA = detrended fluctuation analysis, LRTCs = long-range temporal correlations

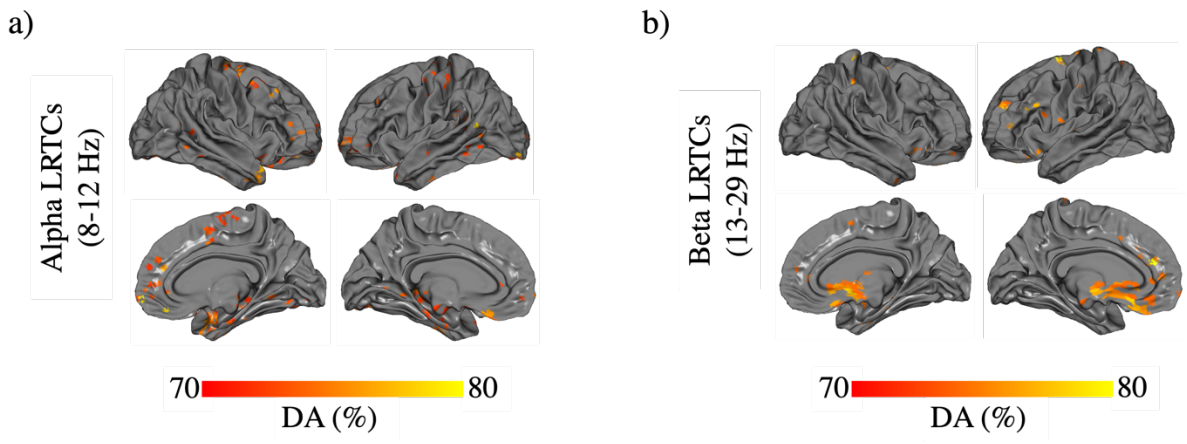


FIGURE 7: CLASSIFICATION OF SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS IN THE CORTEX

SVM used alpha (a) and beta (b) DFA exponents (LRTCs) as discriminant features at the cortical level. The images are thresholded at statistically significant decoding accuracy ($p<0.005$, permutation tests and max statistics correction). DA = decoding accuracy, DFA = detrended fluctuation analysis, LRTCs = long-range temporal correlations, SVM= support vector machine

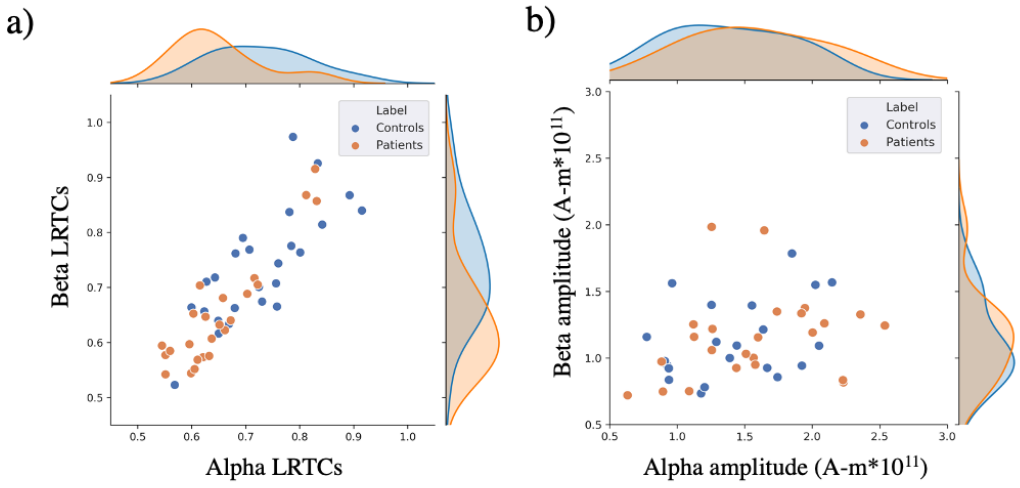


FIGURE 8: SCATTER PLOT VISUALIZATION OF INDIVIDUAL LRTC AND AMPLITUDE VALUES IN BRAIN REGIONS WITH STATISTICALLY SIGNIFICANT CLASSIFICATION

(A) illustrates individual LRTC values, averaged across all the nodes that showed statistically significant patient vs controls decoding in the alpha and beta frequency bands (n=50). (B) illustrates individual amplitude values (A-m*10^{-11}) in the alpha and beta in the same brain regions (n=46, data from 4 outliers were excluded due to amplitude values > 5 std above the mean).

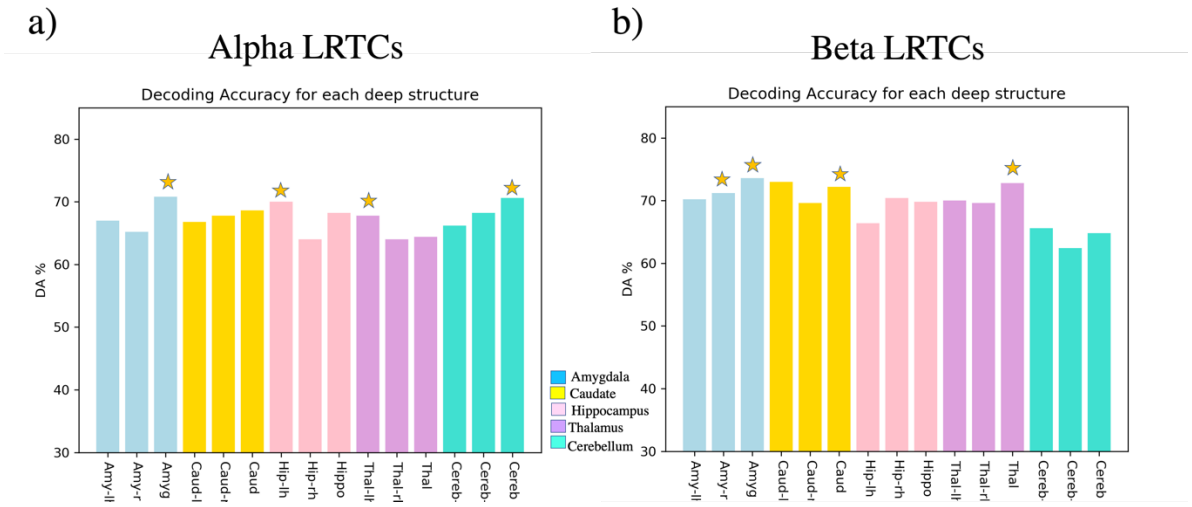


FIGURE 9: CLASSIFICATION OF SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS AT THE SUB-CORTICAL LEVEL

SVM used alpha (a) and beta (b) DFA exponents (LRTC) as discriminant features computed in deep structure ROIs. Statistically significant decoded ROIs are indicated with a star ($p<0.001$). The suffix "-lh" indicates left hemisphere, "-rh" indicates right hemisphere, and no suffix reflects classification using both left and right hemispheres. Amy = amygdala, Caud = caudate, Cereb = cerebellum, DA = decoding accuracy, DFA = detrended fluctuation analysis, Hipp = hippocampus, LRTCs = long-range temporal correlations, SVM= support vector machine, Thal = thalamus

3.3.2 Group comparisons of spectral amplitude

To appreciate the putative value of LRTC features, we also computed the same contrasts and classification using, the more standard, spectral amplitude as feature. Figure 10 shows both increased and decreased oscillatory amplitudes among schizophrenia patients compared to controls. Conventional t-tests of the amplitude did not yield any significant group differences after multiple comparison correction in any of the frequency bands ($p>0.05$ for two-tailed tests). Nevertheless, Figure 10 shows the t-values to indicate the direction of the group differences in terms of amplitude magnitude, with the negative (blue) t-values showing brain areas where patients have reduced amplitude compared to controls, and the positive (red) t-values showing brain areas where patients have increased amplitude compared to controls. This was also the case when using SVM classification in all frequency bands, except for the gamma-band oscillatory amplitude, which led to a statistically significant classification (Figure 11). In particular, gamma-band oscillations led to statistically significant discrimination in the orbital sulci and gyri,

parahippocampal gyri, temporal poles, left superior temporal sulcus, and left temporal gyrus, with patients showing higher spectral amplitude levels in these given brain structures. The highest discrimination occurred in the left temporal pole with a decoding accuracy of 84% (Figure 11, max statistics correction, $p<0.005$).

Figure 12 shows the classification results of schizophrenia and controls using the alpha (Figure 12a), beta (Figure 12b) and gamma (Figure 12c) bands oscillatory amplitude in the deep structures. In terms of subcortical structures, the gamma-band amplitude of the left caudate significantly decoded the two groups, as well as the amygdala (using the left, right, and both hemispheres), hippocampus (using the left and both hemispheres) and cerebellum (using both hemispheres) (72-79%, max statistics correction, $p<0.001$, Figure 12c).

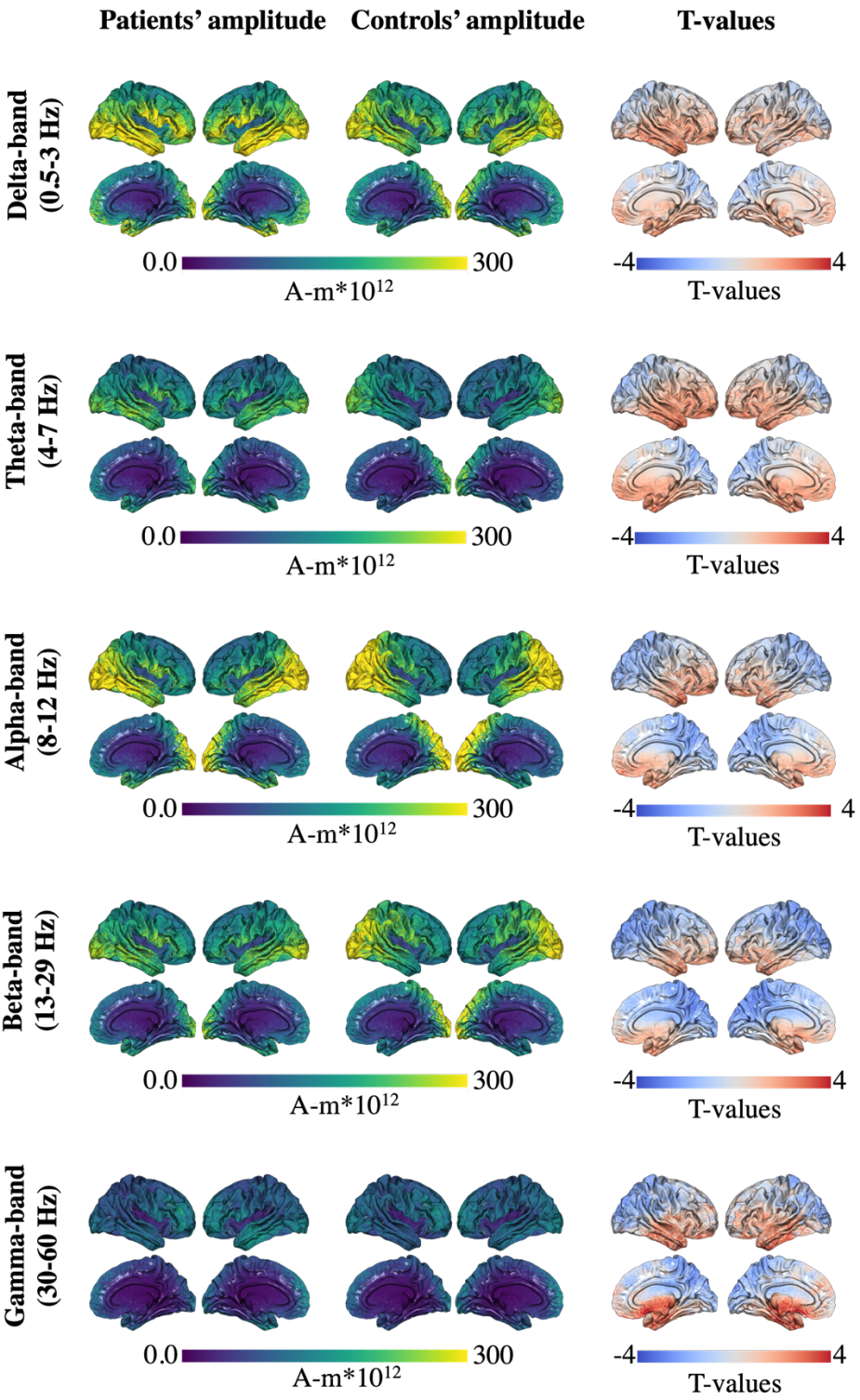


FIGURE 10: SOURCE-LEVEL RESULTS OF SPECTRAL AMPLITUDE OF PATIENTS AND CONTROLS Columns 1 and 2 show averaged amplitude values for each group at each node (A-m $*10^{-12}$). Column 3 shows T-values based on the unpaired t-tests (non-significant).

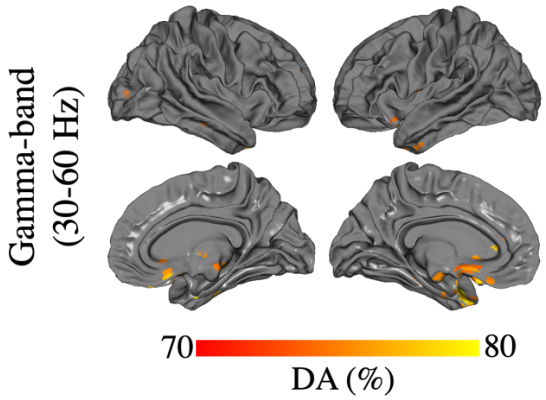


FIGURE 11: SIGNIFICANT CLASSIFICATION OF SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS BASED ON AMPLITUDE

SVM in the spectral amplitude of gamma at the cortical-level significantly classified groups. The images are thresholded at statistically significant decoding accuracy ($p<0.005$, permutation tests and max statistics correction). DA = decoding accuracy, SVM= support vector machine

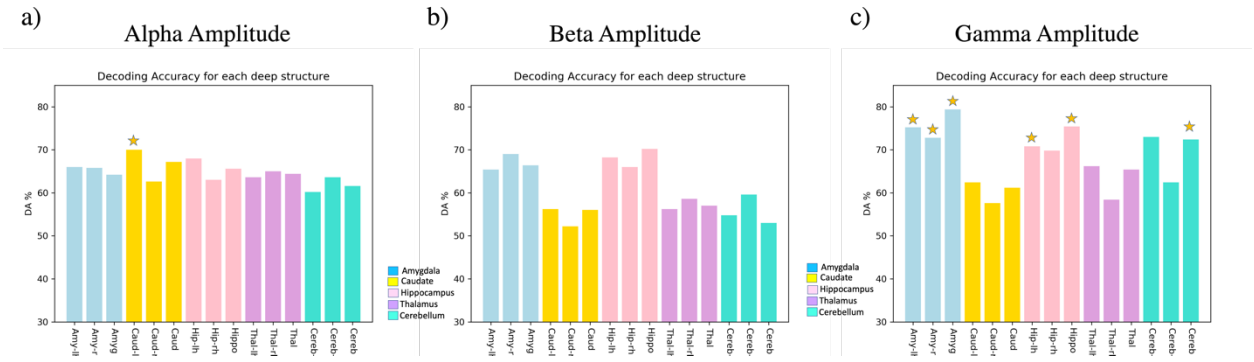


FIGURE 12: CLASSIFICATION OF SCHIZOPHRENIA PATIENTS AND CONTROLS BASED ON SPECTRAL AMPLITUDE AT THE SUB-CORTICAL LEVEL

SVM, with a 10-fold cross validation, applied max statistics and 1000 permutations classified groups. Statistically significant decoded ROIs are indicated with a star ($p<0.001$). The suffix "-lh" indicates left hemisphere, "-rh" indicates right hemisphere, and no suffix reflects classification using both left and right hemispheres. Amy = amygdala, Caud = caudate, Cereb = cerebellum, DA = decoding accuracy, Hipp = hippocampus, LRTCs = long-range temporal correlations, ROI = region of interest, SVM= support vector machine, Thal = thalamus

3.3.3 Correlations with clinical and demographic information

The investigation of the potential correlations between LRTCs and demographic and clinical information yielded no significant results across the five frequency bands. However, the analysis of correlation between amplitude of different frequency bands and schizophrenia patients' negative symptom scores yielded a highly statistically significant result in the theta band (Figure 13). Specifically, spectral amplitude of the delta (Figure 13a) and theta band (Figure 13b) correlated positively with schizophrenia patients' scores on the SANS clinical scale (max correlation $r = 0.81$, $p<0.05$, corrected for multiple comparisons).

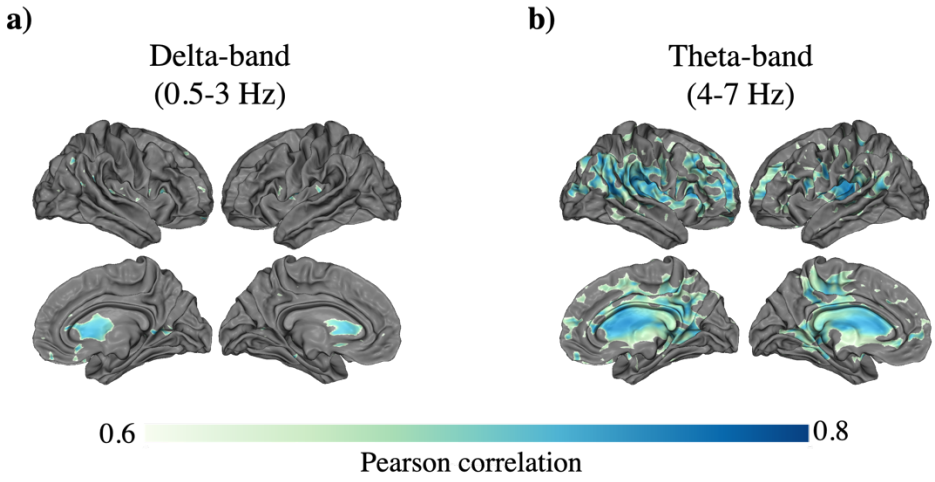


FIGURE 13: CORRELATION BETWEEN SPECTRAL AMPLITUDE AND PATIENTS' SYMPTOMS
Pearson correlation between (a) delta-band amplitude and patients' scores on the scale for the assessment of negative symptoms (SANS), and (b) between theta-band amplitude and SANS scores. The maps are thresholded at a p-value of 0.05, corrected for multiple comparisons.

3.3.4 Summary of eyes open resting-state condition results

Similarly to the eyes closed resting-state condition, LRTCs appeared to be attenuated in schizophrenia patients in the theta, alpha and beta frequency bands, and slightly enhanced in the gamma band, compared to controls (Supplementary Figure 1). With our machine-learning approach, patients and controls were again significantly classified using LRTCs in the alpha and beta frequency bands with up to 79% decoding accuracy (max statistics correction, $p<0.005$, Figure 14a). Specifically, using source-space alpha-band LRTCs as a decoding feature led to

statistically significant discrimination of schizophrenia and controls in the postcentral gyri and sulci, and in the superior temporal gyri and sulci (bilaterally). Moreover, using source-space beta-band LRTCs as a decoding feature let to statistically significant classification of schizophrenia patients and controls in the right precentral gyrus and sulcus, right central sulcus, right postcentral gyrus, right superior-frontal gyrus and paracentral lobules. In terms of subcortical structures, SVM significantly classified (max statistics correct, $p<0.001$) the two groups using alpha-band LRTCs in the left amygdala, left hippocampus and the combination of the left and right hippocampi (Figure 14c and Supplementary Figure 2).

The examination of spectral amplitude in the eyes open condition showed increased oscillatory amplitude in patients in the delta, theta and gamma bands, while a trend of decreased amplitude was seen in the alpha and beta bands (Supplementary Figure 3). Statistical analyses of the amplitude did not reveal any significant group differences in any of the frequency bands. However, machine-learning classification of schizophrenia patients and controls using spectral amplitude yielded significant discriminatory patterns in the delta, theta, beta and gamma bands (Figure 14b). In particular, statistically significant classification of groups were observed in delta-band oscillations in the left postcentral and parieto-occipital sulci and the right temporal pole; in theta-band oscillations in the left parieto-occipital sulcus; in the beta-band in the right orbital and precuneus gyri and temporal pole; and the most significant decoding accuracies were observed in the gamma band, in the left rectus gyrus (88%, max statistics correction, $p<0.005$), along with the right orbital gyrus, orbital sulci and left parahippocampal gyrus. Supplementary Figure 4 shows the classification results of schizophrenia and controls using the alpha, beta and gamma bands oscillatory amplitude in the deep structures. Beta-band amplitude of the right hippocampus significantly decoded the two groups (74%, max statistics correction, $p<0.001$). In terms of gamma oscillations, significant classification (74-78%, max statistics correction, $p<0.001$, Figure 14d and Supplementary Figure 4) of patients and controls were observed in the amygdala (using the left and both hemispheres), the hippocampus (using the left, right, and both hemispheres) and the cerebellum (using the left, right, and both hemispheres).

Finally, in terms of correlation analyses between LRTCs/spectral amplitude and patients' clinical scores, significant correlational results between theta-amplitude and SANS scores were observed,

similar to those in the eye closed condition (max correlation r = 0.81, p<0.05, corrected for multiple comparison, Figure 14e).

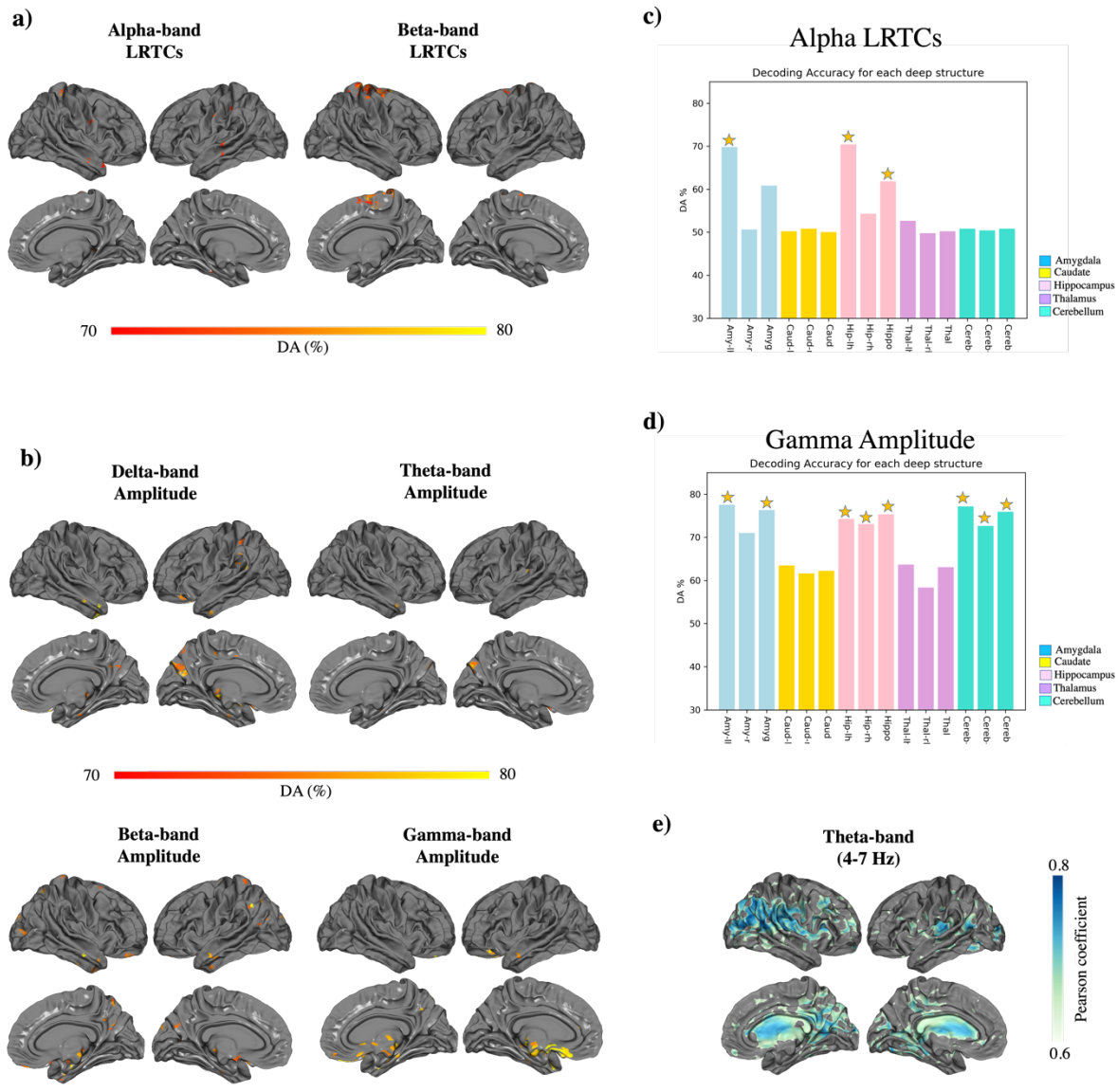


FIGURE 14: SUMMARY OF MAIN RESULTS OF THE EYES OPEN CONDITION

(A) and (c) illustrate statistically significant classification of schizophrenia patients and controls based on LRTCs and amplitude, respectively, at the cortical level (p<0.005, permutation tests and max statistics correction). (B) and (d) illustrate classification of patients and controls based on LRTCs and amplitude, respectively, at the subcortical level. Statistically significant decoded ROIs are indicated with a star (p<0.001). The suffix "-lh" indicates left hemisphere, "-rh" indicates right hemisphere, and no suffix reflects classification using both left and right hemispheres. (E) Pearson correlation between theta-band amplitude and patients' scores on the SANS, p-values are corrected for multiple comparisons, p<0.05." Amy = amygdala, Caud = caudate, Cereb = cerebellum, DA = decoding accuracy, Hipp = hippocampus,

LRTCs = long-range temporal correlations, ROI = region of interest, SANS = Scale for the assessment of negative symptoms, Thal = thalamus

3.3.5 Comparison of eyes closed and eyes open resting-state conditions

Within-group, statistical comparisons of the eyes open and eyes closed conditions revealed a cortex-wide attenuation of LRTC values in the alpha and beta band for controls in the eyes open condition, compared to eyes closed (paired t-tests, max stat correction, 1000 permutations, $p < 0.05$). However, in the case of schizophrenia patients, this LRTC difference between eyes open and closed was not statistically significant, although it did appear that LRTC values were higher in the eyes closed than in the eyes open condition.

In terms of amplitudes differences, paired t-tests showed that amplitude magnitudes of the alpha-band were substantially higher in the eyes closed condition than the eyes open condition for both schizophrenia patients and healthy controls, particularly in the temporal and visual cortices, as expected. This difference was even bigger in schizophrenia patients, as the occipital lobe differences were statistically significant after multiple-comparison correction ($p<0.05$, max stat, 1000 permutations).

3.4. Discussion

Although widely studied, the neural mechanisms underpinning the symptomology of schizophrenia are still somewhat elusive. Given that correct diagnosis and early treatment is crucial for medication adherence and good prognosis, the clinical research community has focused on identifying characteristics that are unique to this pathology. To address this, the leading theory of neural dysconnectivity has been explored extensively in the spatial domain, but very little has been discussed in terms of *temporal* dysconnectivity in schizophrenia. The aim of this study was to explore whether schizophrenia-specific differences exist within the temporal structure of neural oscillations, during resting-state, using MEG measurements to probe both cortical and subcortical brain regions. Our results show that this is indeed the case. This finding corroborates and extends previous studies that have observed both healthy and pathological brain-signals to exhibit DFA exponents that were between 0.5 and 1 (Linkenkaer-Hansen et al., 2001b, 2004; Nikulin and

Brismar, 2004, 2005; Berthouze et al., 2010; Fedele et al., 2016). While the resting neural system exhibited temporal persistence (scaling exponent above 0.5), indicating that the structure of the brain signal was maintained through time for both groups, the weaker exponents found in schizophrenia patients suggest a loss in persistence (or memory) in the signal. This drop from values close to 1 towards 0.5 is reflective of near-uncorrelated signals (Peng et al., 1995; Linkenkaer-Hansen et al., 2001b) and has often been thought to be indicative of diminished regularity (Beggs and Timme, 2012) and a change in the neuronal excitability-inhibitory balance (Poil et al., 2012; La Rocca et al., 2018). This might be due to changes in NMDA-receptor conductance, which in-turn would increase the variability of a signal, decrease the stability of the signal's memory, and increase the chance for a change in state (e.g. order to disorder) (Loh et al., 2007; Rolls et al., 2008).

Furthermore, the attenuated temporal auto-correlations in schizophrenia were confined to the alpha and beta envelopes in distinct cortical and subcortical areas. Indeed, single-feature SVM classification was able to successfully differentiate the two groups with up to 82% decoding accuracy, solely based on the measure of LRTCs. In the alpha-band, the brain areas that significantly contributed to the classification of patients and controls included the pre and post central gyri and sulci, temporal poles, temporal gyrus and the parahippocampal gyri. In the beta-band, these regions included the orbitofrontal cortices, the anterior cingulate gyri and sulci, the left insula and the right parahippocampal gyrus. Structural (Ohi et al., 2016) and functional (Wang et al., 2015b) alterations of the temporal lobe have been previously highlighted (e.g., reduced grey matter volume). Moreover, the paralimbic areas mentioned above seem to be involved in hallucinations (Silbersweig et al., 1995), as well as the cognitive hypofunctioning in schizophrenia that occurs due to early neurodevelopmental deficits (Liao et al., 2015; Isomura et al., 2017; Xu et al., 2017).

Importantly, the unpreceded analyses of LRTC alterations in subcortical substructures reported here provides the first evidence that LRTC values computed on alpha and beta band-limited envelopes in deep structures are altered in schizophrenia, to the extent that they allow for robust discrimination between patients and controls in an out-of-sample generalization context (cross-validated machine learning framework). More specifically, statistically significant predictions

(schizophrenia patient vs healthy control) was possible using alpha-band LRTC in the amygdala, left hippocampus, left thalamus and cerebellum, and using beta-band LRTC in the amygdala, caudate and thalamus. Our control analyses of spectral amplitude showed that the observed LRTC alterations were not confounded by differences in oscillatory power. Moreover, the lack of statistical difference in age or gender suggests that the results were not mediated by these demographic information. Despite being a recognized challenge, MEG studies increasingly report activity in subcortical structure (Rivolta et al., 2015; Youssofzadeh et al., 2018) including the amygdala (Lu et al., 2012; Nugent et al., 2015). Alterations in subcortical structures in schizophrenia have been reported in the literature; It is well-known that schizophrenia is associated with pathological changes in thalamic activity (Woodward et al., 2012; Giraldo-Chica and Woodward, 2016). Specifically, the thalamo-cortical dysconnectivity has been pinned as a key player in the cognitive symptoms of patients (Uhlhaas et al., 2013; Chen et al., 2019). In addition, a number of fMRI resting-studies studies have discussed the implication of the hippocampus, amygdala, caudate and cerebellum in the pathophysiology of schizophrenia. Of particular interest, the observed beta-band LRTC alterations in the amygdala is consistent with previously reported amygdala changes at the structural (Rajarethinam et al., 2001; Velakoulis et al., 2006) and functional/connectivity levels (Mukherjee et al., 2013). This limbic area is implicated in social cognition (Adolphs, 2002) and damage to it can lead to aberrant social judgement, similar to what is seen in schizophrenia.

With respect to spectral amplitude, our findings confirm previous studies that observed increased power in resting-state MEG gamma-band oscillations in schizophrenia patients (Venables et al., 2009; Gandal et al., 2012; Andreou et al., 2014, 2015; Di Lorenzo et al., 2015; Mitra et al., 2015; Northoff and Duncan, 2016; White and Siegel, 2016). SVM was able to successfully classify the two participant groups based on gamma-band amplitude in the orbital cortex, parahippocampal gyri, temporal cortex, amygdala, hippocampus and cerebellum. However, no significant amplitude differences were observed in the alpha and beta frequency bands, where the prominent LRTC changes were found. This rules-out any speculations that the LRTC alterations in schizophrenia are driven by the effect or magnitude of spectral amplitude. It should be noted that, although ocular movement-related artefacts were removed using ICA, it is possible that some of the gamma-band

amplitude differences, and thereby the gamma amplitude decoding results, could in part be due to uncaptured eye motion in patients.

Correlational analyses looking at LRTCs and patients' clinical information yielded no significant results. In terms of amplitude however, we observed a strong positive correlation between the theta-band amplitude and SANS score. The brain regions involved in this finding were comprised of the parieto-temporal lobes, bilaterally. This result is in-line with previous studies that have observed enhanced resting low-frequency activity (Fehr et al., 2001, 2003; Sperling et al., 2002; Wienbruch et al., 2003; Chen et al., 2016), as well as positive correlations between low frequency oscillations and patients' negative symptoms (Chen et al., 2016; Fehr et al., 2003; Jandl et al., 2005; Venables et al., 2009; review: Boutros et al., 2014). Unlike the recent publication by (Zeev-Wolf et al., 2018), however, correlations between alpha or beta-band power and patients' symptoms scores were not significant. This could be due to the way the authors divided their patient group into high and low negative scores, and high and low positive scores, while we did not perform such separation of our participants, particularly since our patient group was fairly asymptomatic. It is also possible that this difference is due to our smaller sample size, or our statistical thresholds and the strict correction that we applied for our comparisons.

Our robust and statistically significant machine-learning findings highlight the potential of using scaling dynamics as an early biomarker of schizophrenia. During typical development, LRTCs appear to increase and strengthen during the transition from childhood to adolescence (Smit et al., 2011). This phase is also a critical period during which psychopathologies typically arise (van den Heuvel and Kahn, 2011). Thus, we hypothesized that diminished LRTCs in patho-relevant areas could potentially reflect neural alterations during brain maturation among schizophrenia patients that parallel those of excess synaptic-pruning, which lead to reduced gray matter volume (Uhlhaas, 2011). Indeed, both reduced gray matter volume (Witthaus et al., 2009) and white matter (Quan et al., 2013) have been reported in the same brain regions where we found diminished LRTCs (e.g., inferior frontal gyrus, which is thought to relate to core executive functions, such as inhibitory response) (Swick et al., 2008). Future longitudinal research that includes MEG recordings in large cohorts of individuals at-risk of developing psychosis is recommended to further the findings of the present study.

Comparison of the eyes open and eyes closed conditions revealed that LRTC values were overall higher in the eyes closed than in the eyes open condition, particularly for healthy controls and less so for schizophrenia patients. This result is opposite to the one reported by (Sun et al., 2014), who did not find significant differences between eyes open and closed in healthy controls' LRTCs. With respect to schizophrenia patients, their LRTCs values were more similar, perhaps because the reported LRTCs values were lower to begin with (and already close to the lower-bound value of 0.5) compared to controls. Interestingly, our LRTC findings in the beta-band (eyes open condition) were consistent with that of a recent EEG paper by (Moran et al., 2019). While it is unclear why substantial differences in LRTCs exist in the eyes open and eyes closed conditions, we hypothesize that differential neural mechanisms are at work, and thus bring about differences in the temporal structure of neural activity. It is tempting to hypothesize that when healthy participants close their eyes, they reach a more relaxed state, which in turn allows for better signal memory and autocorrelation in the system. Conversely, this state is perhaps harder to attain for schizophrenia patients who exhibit more neuronal excitability (scaling exponents closer to 0.5) with their eyes closed. This may partly be in line with the prevalence of sleep-related disorder among schizophrenia patients (Monti and Monti, 2005). It is also noteworthy that the type of instructions given to participants prior to resting-state recordings can influence their neural dynamics (Benjamin et al., 2010; Kawagoe et al., 2018). In the present study, participants let their mind wander during the eyes-open and eyes-closed recordings, thus allowing for a more natural baseline state of rest, compared to potentially more effortful instructions (e.g., "try not to think of anything", Kawagoe et al., 2018).

Taken together, the results of this study characterize, for the first time, temporal dysconnectivity in schizophrenia patients at both the cortical and subcortical levels using MEG. In addition, the machine-learning findings provide good evidence for the use of resting-state LRTCs in alpha and beta frequency bands to confidently discriminate patients from controls.

3.5. Conclusion

In summary, this study shows that models such as the *cognitive dysmetria* and the *disconnection syndrome* can be probed, confirmed and extended using electrophysiological measures of resting neural dynamics (Smart et al., 2015). Indeed, the observed attenuation in temporal autocorrelation in the envelopes of the alpha and beta-band oscillations among schizophrenia patients supports the theory of dysconnectivity from a *temporal* angle. Taken together, this new approach for the quantification of (temporal) dysconnectivity could lead to new venues of research, early diagnosis and treatment for schizophrenia patients.

Chapter 4: Altered brain criticality in Schizophrenia: New insights from MEG

Abstract

Schizophrenia has a complex etiology and symptomatology that is difficult to untangle. After decades of research, important advancements towards a central biomarker are still lacking. One of the missing pieces is a better understanding of how non-linear neural dynamics are altered in this patient population. In this study, the resting-state neuromagnetic signals of schizophrenia patients and healthy controls were analyzed in the framework of criticality. When biological systems like the brain are in a state of criticality, they are thought to be functioning at maximum efficiency (e.g., optimal communication and storage of information) and with maximum adaptability to incoming information. Here, we assessed the self-similarity and multifractality of resting-state brain signals recorded with magnetoencephalography in patients with schizophrenia patients and in matched controls. Our analysis showed a clear ascending, rostral to caudal gradient of self-similarity values in healthy controls, and an opposite gradient for multifractality (descending values, rostral to caudal). Schizophrenia patients had similar, although attenuated, gradients of self-similarity and multifractality values. Statistical tests showed that patients had higher values of self-similarity than controls in fronto-temporal regions, indicative of more regularity and memory in the signal. In contrast, patients had less multifractality than controls in the parietal and occipital regions, indicative of less diverse singularities and reduced variability in the signal. In addition, supervised machine-learning, based on logistic regression, successfully discriminated the two groups using measures of self-similarity and multifractality as features. Our results provide new insights into the baseline cognitive functioning of schizophrenia patients by identifying key alterations of criticality properties in their resting-state brain data.

4.1. Introduction

The global prevalence of schizophrenia is reported to be close to 21 million individuals (Charlson et al., 2018). The symptoms and poor prognosis of those affected can deeply impact their daily functioning, and weigh on those close to them. Unfortunately, progress in therapeutic development is slow in the field of psychiatry due to the extreme complexity of the brain, the heterogeneity of patients' symptoms and difficulties in translational research. More knowledge is needed to better understand what alterations occur in the neural activity of patients. Among the missing pieces, further characterization of the resting neural dynamics of schizophrenia, and their relationship to patients' symptoms, is needed. Alterations in the rhythmic (oscillatory) neural activity of schizophrenia patients have been widely reported in the neuroimaging literature (reviews: Uhlhaas and Singer, 2010; Maran et al., 2016; Alamian et al., 2017). In addition, an emerging body of research has reported changes in the arrhythmic properties of brain dynamics in schizophrenia (Breakspear, 2006; Fernández et al., 2013). A powerful concept that has so far remained under-exploited and poorly understood in neuropsychiatry is criticality.

4.1.1 What is criticality?

The dynamics of many complex systems, such as the human brain, appear to reside around the critical point of a phase transition (Beggs and Plenz, 2003; Stam and De Bruin, 2004; Fraiman and Chialvo, 2012; Palva and Palva, 2018). At this point of criticality, these systems are in a wavering state, at the cusp of a new phase, between the states of order and disorder (Beggs and Timme, 2012; Cocchi et al., 2017; Souza França et al., 2018). The brain requires such a balance of regularity (i.e. structure) on the one hand, to maintain coherent behaviour, and flexibility (i.e. local variability) on the other hand, to adapt to ongoing changes in the environment (R. Chialvo, 2004; Beggs and Timme, 2012). Indeed, critical brain dynamics have been shown to be optimal for fast switching between metastable brain states, for maximizing information transfer and information storage within neural networks (Socolar and Kauffman, 2003; Haldeman and Beggs, 2005), and for optimizing phase synchrony (Yang et al., 2012). Importantly, it is within a critical state that neural communication can span the greatest distance and achieve maximal correlational length (Fraiman and Chialvo, 2012). Thus, the brain's state of criticality is thought to affect the functional

properties of oscillations, local synchronization and signal processing (Palva and Palva, 2018). Changes to this state, due to psychiatric illness for instance, can alter this certain properties of this balance (e.g., in terms of strength and number of synaptic connections) (Beggs and Timme, 2012). Some of the tuning parameters of criticality appear to be embedded in the balance between neural excitation and inhibition (e.g. through NMDA receptors (Mazzoni et al., 2007; Shew et al., 2009; Hobbs et al., 2010; Poil et al., 2012)), in neural network connection strengths, and synaptic plasticity (Rubinov et al., 2011; Beggs and Timme, 2012).

4.1.2 Measures of criticality

4.1.2.1 Self-similarity and multifractality

Within the framework of criticality, local and large-scale fluctuations arise from excitatory post-synaptic potentials (EPSPs) and modulate brain states by facilitating or suppressing neuronal firing (Palva and Palva, 2018), with long-range spatial spread (He et al., 2010; Zilber, 2014). Systems in this state are characterized by power-law distributions, fractal geometry and fast metastable state transitions (Plenz and Chialvo, 2009; Cocchi et al., 2017; Chialvo, 2018; Palva and Palva, 2018). These features of a critical state are said to be scale-free or scale invariant. Power-law distributions of a given signal can be recognized as a linear slope in the log-log plot of the feature distribution, and they imply that the signal‘s statistics and structural characteristics are preserved across spatiotemporal scales—in other words, that the signal has fractal properties (Beggs and Plenz, 2003; Chialvo, 2018). Fractal architectures describe objects that contain identical, or statistically-equivalent, repetitive patterns at different magnifying scales (Mandelbrot, 1983, 1985; Van Orden et al., 2012; Fetterhoff et al., 2015).

Scale invariant dynamics of systems at criticality (i.e., power-law distributions and fractal architecture) have often been described using a $1/f^{\beta}$ power law fitted to Fourier-based spectral estimations. On the other hand, self-similarity is a well-accepted model for scale-free dynamics and is richer than the sole measure of β, as it captures fractional Gaussian noise and fractional Brownian motion. Self-similarity can be measured by the Hurst exponent, H. In the brain, H is thought to index how well neural activity is temporally structured (via its autocorrelation). The smoother the signal, the higher the value of H (Zilber, 2014). However, self-similarity alone does

not fully account for scale-free dynamics or criticality, since it can only capture additive processes (La Rocca et al., 2018). Combining self-similarity with multifractality improves on this framework to better capture criticality in a system. Multifractality can account for the remaining non-additive, non-Gaussian processes. The multifractality parameter, *M,* quantifies the diversity of *H*'s (singularities) and the overarching geometry of spatiotemporal fluctuations (Leonarduzzi et al., 2016; La Rocca et al., 2018). Generally, fractals are evaluated using the topological dimension, *D*, which describes the complexity and structure of an object by measuring the change in detail based on the change in scale (Di Ieva, 2016). In multifractal analysis, the local regularity of a signal is quantified using the *Hölder exponent, D(h)* (Jaffard et al., 2016), allowing a more realistic characterization of phenomena that are too complex to be explained solely by Euclidian models. In sum, the brain's degree of criticality is defined by its scale-free dynamics, which are best quantified by combining measures of self-similarity and multifractality.

4.1.2.2 Common measures of criticality

Numerous metrics have been developed to measure the scale-free properties that define criticality, such as Detrended Fluctuation Analysis (DFA) applied to oscillatory envelopes (Linkenkaer-Hansen et al., 2001a; Hardstone et al., 2012) and neuronal avalanche detection (Beggs and Plenz, 2003). Non-linear dynamics, and specifically multifractal analysis, has been used to address questions of self-similarity and multifractality. Multifractal analysis can characterize both the amount of global self-similarity in a system and the amount of local fluctuations (i.e. number of singularities) (Zilber et al., 2012). This approach allows for more in-depth interpretations of the electrophysiological data compared to more conventional analytical approaches. A number of mathematical frameworks have tapped into this, such as the Multifractal Detrended Fluctuation Analysis (MFDFA; (Kantelhardt et al., 2002; Ihlen, 2012)) and the Wavelet Leaders-based Multifractal Analysis (WLMA; (Wendt, 2007; Wendt and Abry, 2007; Serrano and Figliola, 2009)). For reviews of scale-free and multifractal analytical approaches, see (Lopes and Betrouni, 2009; Zilber, 2014).

4.1.2.3 Application to psychiatry

The application of criticality models to psychiatry, and in particular to the study of schizophrenia (SZ), is well in line with leading theories for this pathology, which are centered around

dysconnectivity and altered information processing and transfer (Weinberger et al., 1992; Friston and Frith, 1995; Fernández et al., 2013). So far, most of the empirical evidence for dysconnectivity theory in SZ has come from functional magnetic resonance imaging studies, which highlight several important alterations in anatomical and functional connectivity that exist in SZ patients, as well as from electroencephalography (EEG) and magnetoencephalography (MEG) connectivity studies (review: (Alamian et al., 2017b)). However, we still lack a complete, in-depth understanding of the brain alterations inherent to this pathology in the temporal domain.

In terms of scale-free analyses in psychiatry, power spectral densities (PSD) of resting-state fMRI scans have shown SZ patients to have reduced complexity and disrupted scale invariant dynamics compared to controls in the precuneus, inferior frontal gyrus and temporal gyrus, and these changes correlated with their symptoms (Lee et al., 2020). Electrophysiological studies have found altered dimensional complexity and increased variability in SZ patients' signal (Koukkou et al., 1993). A number of studies have applied different versions of multifractal analysis on electrophysiological (Slezin et al., 2007b; Racz et al., 2020) or white-matter MRI data in SZ (Takahashi et al., 2009). One of these used the multifractal analysis on resting-state EEG data, and found increased long-range autocorrelation and multifractality in patients compared to controls (Racz et al., 2020).

In addition, two insightful reviews have examined how non-linear methods could improve our understanding of SZ (Breakspear, 2006; Fernández et al., 2013). They highlighted conflicting results among studies reporting on complexity changes in SZ, which they proposed were attributable to participants' symptomatic state, the method of imaging or medication. Complexity as measured by Lempel–Ziv complexity (LZC) or correlation dimension (D2) was typically found to be increased in SZ in studies that recruited younger, first-episode patients who were drug-naïve and symptomatic, while studies reporting SZ-related reductions in complexity tended to recruit older, chronic, patients who were on medication and hence less symptomatic (Lee et al., 2008; Fernández et al., 2013). Although these measures have been widely applied to neuroscientific data, they each come with caveats that affect their precision or generalizability. Moreover, these reviews highlight the importance of controlling for factors such as age and medication when studying complex pathologies, such as SZ.

4.1.3 Goals of the study

The brain is functionally optimal when in a state of criticality—in other words, when neural activity can spread equally well at long and short distances in time and space and information is processed and stored efficiently (Shew et al., 2009)—and multifractality analysis is among the most reliable indicators of criticality. Meanwhile, leading neural theories of SZ emphasize a pathological spatiotemporal dysconnectivity. It follows that the potential insights to be gained from multifractal analysis in SZ is extensive.

Therefore, the aim of the present study is to examine how criticality is altered in the neural activity of chronic SZ patients using the high temporal resolution of resting-state MEG data, the spatial resolution of structural MRI and wavelet-based estimations of multifractality and self-similarity. We also assessed the predicative power of criticality features in classifying patients and controls using supervised machine-learning. We hypothesize that, compared to healthy controls, chronic SZ patients will exhibit reduced self-similarity in the prefrontal cortex and increased self-similarity in sensory brain regions, along with reduced multifractality overall. We also predict significant correlations between measures of criticality and patients' clinical symptom scores.

4.2. Materials and methods

4.2.1 Participants

Participant data collection was conducted at the Cardiff University Brain Research Imaging Centre in Wales, U.K., and the data analyses were conducted at the University of Montreal, QC, Canada. Ethical approval was obtained for the data collection according to the guidelines of the United Kingdom National Health Service ethics board, and the Cardiff University School of Psychology ethics board (EC.12.07.03.3164). Ethical approval was also obtained for these analyses from the research committee of the University of Montréal (CERAS-2018-19-069-D).

Behavioural and neuroimaging data from 25 chronic SZ patients (average age = 44.96 ± 8.55, 8 females) and 25 healthy controls (average age = 44.04 ± 9.20, 8 females) were included in this

study. Healthy controls had no history of psychiatric or neurological disorders. The collected demographic information from all participants included: age, gender, depression score on the Beck Depression Inventory – II (BDI-II (Beck et al., 1996)), and mania score on the Altman Self-Rating Mania Scale (ASRM (Altman et al., 1997)). For the SZ patient group, additional information was collected: scores on the Scale of the Assessment of Positive Symptoms (SAPS) and the Scale of the Assessment of Negative Symptoms (SANS) (Kay et al., 1987), and information on antipsychotic doses standardized using olanzapine equivalents (Gardner et al., 2010). All of these data were anonymized, such that no identifiable information of participants was associated with their data nor with data from subsequent analyses. Patients were overall fairly asymptomatic on the testing day. No statistically significant group differences were observed across these demographic and clinical metrics, except for BDI-II scores, where SZ patients had on average mild depression (14.83 ± 9.11), compared to controls (4.50 ± 4.67). Additional details on participant information (i.e., recruitment procedure, exclusions, inclusions, and sample size calculation) can be found in Chapter 3 (Alamian et al., 2020).

4.2.2 MEG and MRI experimental designs

For this study, the brain imaging data consisted of five-minutes of resting-state MEG signal, recorded during an eyes-closed condition, with a 275-channel CTF machine. Reference electrodes were placed on each participant to account for cardiac, ocular and other potential artefacts (Messaritaki et al., 2017). The MEG signal was initially recorded at a sampling frequency of 1200Hz. To conduct the MEG source reconstruction analysis, individual anatomical-T1 MRI scans were also recorded for each participant.

4.2.3 Data preprocessing and MEG source reconstruction

NeuroPycon (Meunier et al., 2019), an open-source python pipeline, was used for the preprocessing and source-reconstruction analyses. First, the continuous raw data was down-sampled from 1200Hz to 600 Hz, and band-pass filtered between 0.1-150 Hz. Next, independent component analysis (ICA) was used to remove artefacts from the MEG signal using MNE-python (Hyvarinen, 1999; Gramfort et al., 2013).

Since it has been reported that the values of the Hurst exponent, *H*, are unusually low in sensor-space, and tend to increase when moving from sensor to source space (based on simulations and real data: (Blythe et al., 2014)), source-reconstruction steps were taken to present cortical-level results in multifractal analysis. To generate individual anatomical source-spaces, the anatomical T1-MRI information of each subject was segmented with FreeSurfer (Fischl, 2012). However, given that this process would produce different source-space dimensions for each participant, individual source spaces were morphed and projected onto a standardized space from FreeSurfer (*fsaverage*) (Greve et al., 2013). The resulting source-space comprised 8196 nodes on the cortical surface, where dipoles were 5mm apart. The single layer model boundary element method implemented in MNE-python was used to compute the lead field matrix (Gramfort et al., 2013). Weighted Minimum Norm Estimate (Dale and Sereno, 1993; Hämäläinen and Ilmoniemi, 1994; Hincapié et al., 2016), implemented in the MNE-python package (Hyvarinen, 1999; Gramfort et al., 2013), was used to compute the inverse solution with a Tikhonov regularization parameter of *lambda* = 1.0 (Hincapié et al., 2016). Dipoles of the source-space were constrained to have an orientation perpendicular to the cortical surface. Thus, for this study, 8196 time series were extracted at the cortical level.

4.2.4 Characterization of criticality through self-similarity and multifractality

4.2.4.1 Measuring self-similarity and multifractality

The singularity spectrum is a concise way to summarize information about scale-free dynamics. It allows the plotting of the Hölder exponents (*h*) about local variability in a time series, against the Fractional (Hausdorff) Dimensions, *D(h)*, as can be seen in Figure 15.

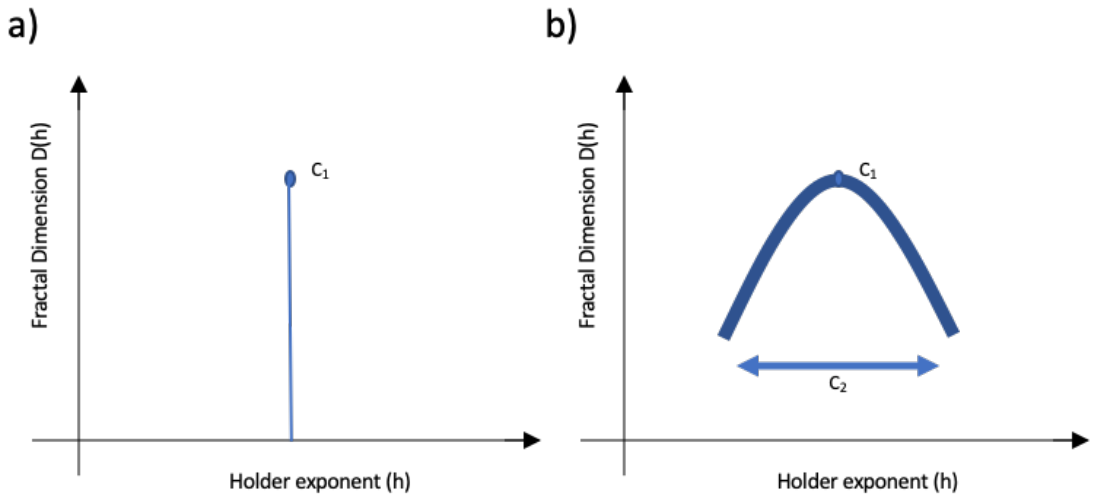


FIGURE 15: SKETCH OF A SINGULARITY SPECTRUM
These sketches illustrate the multifractal scaling function, which depicts a singularity spectrum. Local variability in the signal is represented by Hölder exponents, h, on the x-axis, while the amount of singularities is represented by the Fractal Dimension, D(h), on the y-axis. The apex of the curve reveals the most common h exponent, while the width of the curve reveals the multifractal spectrum. Using log-cumulants from the WLBMF (described in 2.4.2) to describe the singularity spectrum, C1 informs on the apex, while C2 informs on the width of the function. Panel (A) shows a monofractal function, where C1=H and C2 = 0, and panel (B) shows a multifractal function, where the concavity shows the distribution of h singularities.

Multifractal analysis builds on measures of self-similarity (e.g., slope of the PSD, DFA) to provide information about local fluctuations (singularities) in time. The multifractality spectrum and the scaling function ζ(q) (in terms of statistical moments *q*) are related, and can be described using the Legendre transformation:

$$D(h) = \frac{min}{q \neq 0}(1 + qh - \zeta(q)).$$

When a signal is monofractal, this becomes a linear function, where ζ(q) = qH, as it would only have a single singularity (one unique property, Figure15a). Here, the self-similarity parameter would be equal to *H*, the Hurst exponent (Wendt et al., 2007). When a signal is multifractal, the function ζ(q) has a curvature, as in Figure 15b, which shows the global spectrum of singularities. The Hölder exponent (*h*) with the largest Fractal dimension, *D,* (apex of the curve) is said to be the most common singularity in the time-series. The width of the curve can be described with the multifractality parameter, *M* (Wendt et al., 2007).

In this study, to meaningfully estimate self-similarity and multifractality, we used the Wavelet p-Leader and Bootstrap based MultiFractal analysis (WLBMF). This approach builds on the Wavelet leaders-based multifractal analysis (WLMA) method that has been thoroughly described elsewhere (Wendt, 2007; Wendt et al., 2007; Serrano and Figliola, 2009; Ciuciu et al., 2012; Fetterhoff et al., 2015). Briefly, this WLMA method of estimating the singularity spectrum was shown to be efficient in untangling the scaling properties of neuronal signal, and more robust than other algorithms in addressing non-stationarity issues (Wendt, 2008). The curved shape of the scaling function ζ(q) can be written in its polynomial expansion around its maximum to allow the evaluation of C_p, log-cumulants:

$$\zeta(q) = \sum_{p=1}^{\infty} C_p \left(\frac{q^p}{p!}\right).$$

The singularity spectrum can be thus derived from the series-expansion of C_p. The first two log-cumulants are the most informative, with C1, the first log-cumulant, reflecting self-similarity (and the location of the maximum of *D(h),* similar to *H*). Its values approximate those of the *H*; values above 0.5 indicate positive correlation (signal has memory), values below 0.5 indicate negative correlation, and a value of 0.5 indicates lack of correlation (random signal). Meanwhile, C2, the second log-cumulant, reflects multifractality (and the width of the singularity spectrum, like *M*) (Wendt, 2007; Wendt et al., 2009; Zilber, 2014; Diallo and Mendy, 2019). Given the concavity of the scaling function, C2 is always negative, and when C2 equals 0, it is said to indicate monofractality.

Hölder exponents cannot take on negative values. Thus, most multifractal analyses are constrained to scaling functions that have only positive local regularities, implying that there is a continuous temporal positive correlation in the signal (i.e., locally bound everywhere in the function). However, this is not true of all brain signals, which can present with discontinuities in the signal and can thus take on negative regularities. Thus, p-leaders have been proposed as a way to circumvent this limitation (full description in : Jaffard et al., 2016).

4.2.4.2 Defining parameters of log-cumulants

One method to detect criticality in the brain is through the Wavelet p-Leader and Bootstrap based MultiFractal (WLBMF) analysis and, more specifically, through the evaluation of log-cumulants

(Wendt and Abry, 2007; Wendt et al., 2007). This MATLAB-implemented technique uses the discrete wavelet domain for the analysis of self-similarity and multifractality in signals. In order to compute C1 and C2 in our study, we first plotted the PSD of each participant group (SZ patients, controls) in log-log space and identified the portion of the PSD function exhibiting a log-linear relationship. In our data, the log-linear portion of the PSD belonged to j1=7 and j2=10, which correspond to 3.5 Hz and 0.4 Hz, respectively, as deduced by the following equation: Scale $= \frac{3 \times Sf}{4 \times 2^j}$, where Sf represents the sampling frequency, j1 and j2 represent the start and end points of the log-linear portion, respectively, and the scale represents the frequency bin to which it corresponds. This frequency range is similar to those of other researchers who have used the same multifractal analysis (Zilber, 2014). The PSD was calculated at the overall cortical level and also at the ROI level, using the Destrieux Atlas (Destrieux et al., 2010), to ensure that the linear part of the spectrum remained the same across brain regions. For the purposes of this study, we used second order statistics in the evaluation of the log-cumulants (i.e., p-leader of p=2), corresponding to long-range temporal correlations computed with DFA (Leonarduzzi et al., 2016). For the ROI-based investigations, the C1 and C2 log-cumulants were first computed for each node (n=8196 sources) in cortical source-space, and then averaged across ROIs (n=148 ROIs based on the Destrieux atlas, (Destrieux et al., 2010)).

4.2.5 Statistics and machine-learning analyses

4.2.5.1 Conventional statistics and correlation analyses

Group statistical analyses were conducted between SZ patients and matched-controls to test for group-level differences in C1, C2, and demographic and clinical data. This was done at the ROI and source levels. To do so, we used non-parametric statistical tests (two-tailed, unpaired, pseudo t-tests), corrected with maximum statistics using permutations ($n = 1000$, $p < 0.001$) (Nichols and Holmes, 2001; Pantazis et al., 2005).

Moreover, Pearson correlations with False Discovery Rate (FDR) correction (Genovese et al., 2002) were used to explore the relationship between cortex-level C1/C2 values and scores on the SANS, SAPS and medication-dosage, in patients. FDR correction (Benjamini-Hochberg) was

applied to each p-value (computed for each of the 8196 nodes) to account for the multiple comparisons in order to achieve a significance threshold of $p<0.05$, corrected

4.2.5.2 Machine learning analyses

MEG signal classification was conducted using a logistic regression model and a stratified 10-fold cross-validation scheme to evaluate the discriminative power of the log-cumulants C1 and C2 in classifying SZ patients and controls. First, at each of the 8196 nodes, the feature vector (either C1 or C2 values), computed for each participant, was split into 10 folds, while maintaining a balance between the two classes (SZ and controls). Next, the classifier was trained on the data from nine of the ten folds and tested on the remaining fold (test set). The classification performance was assessed using the decoding accuracy (DA) on the test set (i.e., percentage of correctly classified participants across the total number of participants in the test set). This operation was repeated iteratively until all the folds were used as test sets. The mean DA was used as the classification performance metric. In order to infer the statistical significance of the obtained DAs, permutation tests were applied to derive a statistical threshold as described in (Combrisson and Jerbi, 2015). This method consists of generating a null-distribution of DAs obtained by running multiple instances of the classification (n=1000), and randomly shuffling class labels each time. Maximum statistics were applied in order to control for multiple comparisons across all the nodes (Nichols and Holmes, 2001; Pantazis et al., 2005). Visbrain was used for all the ROI and cortical-level visualizations (Combrisson et al., 2019).

4.3. Results

4.3.1 Alterations in self-similarity and multifractality

The group averages of C1 and C2 values for schizophrenia patients and healthy controls can be seen in Figure 16. Across both participant groups, a clear gradient in C1 values is observed, which increases from the frontal lobe to the occipital lobe. Interestingly, a similar gradient, but in the opposite direction, is observed in terms of C2 values in both groups, with C2 values gradually increasing from the occipital lobes to the frontal lobes. Moreover, these gradients appear less pronounced in patients than in controls.

Conventional unpaired t-tests between the two subject groups did not yield any statistically significant differences in terms of C1 or C2 values ($p<0.05$, two-tailed t-test). Nevertheless, in Figure 17a, the t-values show the direction and magnitude of group differences in term of C1 and C2 values, with the positive (red) t-values showing brain areas where patients have smaller C1 or C2 values compared to controls, and the negative (blue) t-values showing brain areas where patients have larger C1 or C2 values compared to controls.

By contrast, when using a machine-learning approach to test for out-of-sample generalization in the same data, we found that C1 and C2 in multiple brain regions led to statistically significant classification of the two subject groups, with up to 77% decoding accuracy (Figure 17d, max statistics correction, $p<0.05$). More specifically, using source-space C1 values as a decoding feature led to statistically significant discrimination of SZ and controls in the subcallosal gyrus, middle fontal gyrus and anterior part of the cingulate gyrus, bilaterally. The left superior frontal gyrus, the left inferior frontal gyrus and sulci, and the right orbital, straight and frontomarginal gyri were also significant. The maximum decoding occurred in the left superior frontal gyrus (77%, compared to the chance level of 70%). Meanwhile, using source-space C2 values as a decoding feature led to statistically significant classification of SZ patients and controls in the superior parietal lobule, precuneus and posterior-ventral part of the cingulate gyrus in the right hemisphere. The left post-central gyrus, and superior temporal gyrus and occipital gyrus, bilaterally, were also significant. The maximum decoding accuracy took place in the right temporal gyrus (76%, compared to the chance level of 70%). Figures 17b-d show the unthresholded DA values for C1 and C2, as well as the uncorrected results at $p<0.05$, and the corrected classification results at $p<0.05$, with multiple comparisons correction using max statistics.

Figure 18 shows the classification results based on C1 and C2 values computed at the ROI-level ($p<0.05$, corrected for multiple comparisons). The ROIs involved in the significant discrimination of patients and controls were the left straight gyrus, the triangular part of the inferior frontal gyrus and the medial transverse frontopolar gyrus and sulcus for C1, and the superior occipital gyrus, the right cuneus and the left angular gyrus for C2. To illustrate how the classifier was able to successfully separate SZ patients from healthy controls, individual C1 and C2 values were computed and averaged across all brain sites that had shown significant decoding at the source-

level. These values are presented in a scatter plot in Figure 19. The distribution of the individual C1 and C2 values (averaged over all sources with significant decoding accuracy) shows that C1 values are higher in patients than in controls (i.e. a trend towards more self-similarity) and C2 values also shift upwards in patients (i.e. a trend towards less multifractality).

It is noteworthy that this scatter plot reveals the presence of positive C2 values in the dataset, primarily in patients. Although mathematically ill-defined, the observation of positive C2 is not unprecedented. Positive C2 values in some individuals can be attributed to numerical instabilities (and might be statistically undistinguishable from 0) or to the fact that the data in these participants cannot be modeled using the multifractal formalism. The safest interpretation for the positive C2 values observed in Figure 19 (primarily in patients), is that data in these individuals were neither multifractal ($C2 < 0$) nor monofractal ($C2 = 0$). Given that this specific type of multifractal analysis has never been conducted on clinical data before, we explored how the results would change when using a p-leader of p=4 (as opposed to the p=2 we have used up to now). This analysis found fewer participants to have positive C2 values compared to p=2, and generally allowed for a better modeling of multifractality in the resting neuromagnetic signal of participants. Figures of C1/C2 group averages and classification patterns based on p=4 can be found in the Supplementary material 5. In summary, we observed a similar albeit stronger decoding of patients and controls based on C2 values in p=4 than p=2. Interestingly, C1 values were smaller (Supplementary Figure 5), and the strong frontal lobe classification results based on C1 values at p=2 diminished at p=4 (Supplementary Figure 6 c-d). Taken together, the results of C1 estimation (self-similarity) were more reliable in our data when using a p-leader of p=2, while C2 estimation (multifractality) provided more robust results with p=4. Most importantly, the trends in terms of increasing C1 and C2 values in patients compared to controls was present irrespective of the choice of p.

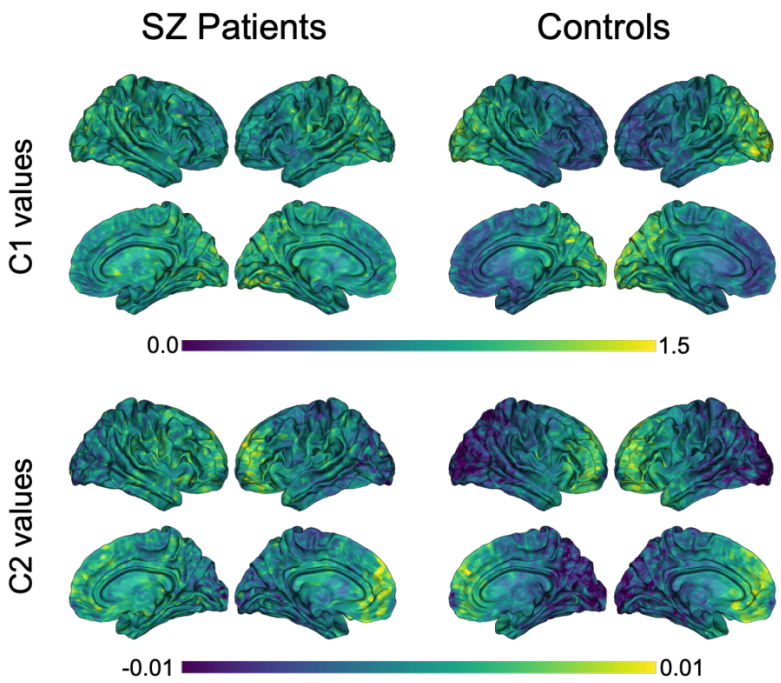


FIGURE 16: GROUP AVERAGES OF C1 AND C2 VALUES IN SZ PATIENTS AND CONTROLS
Averaged C1 and C2 values were computed for each of the 8196 nodes, within each group. P-leader p=2 was used. SZ= schizophrenia

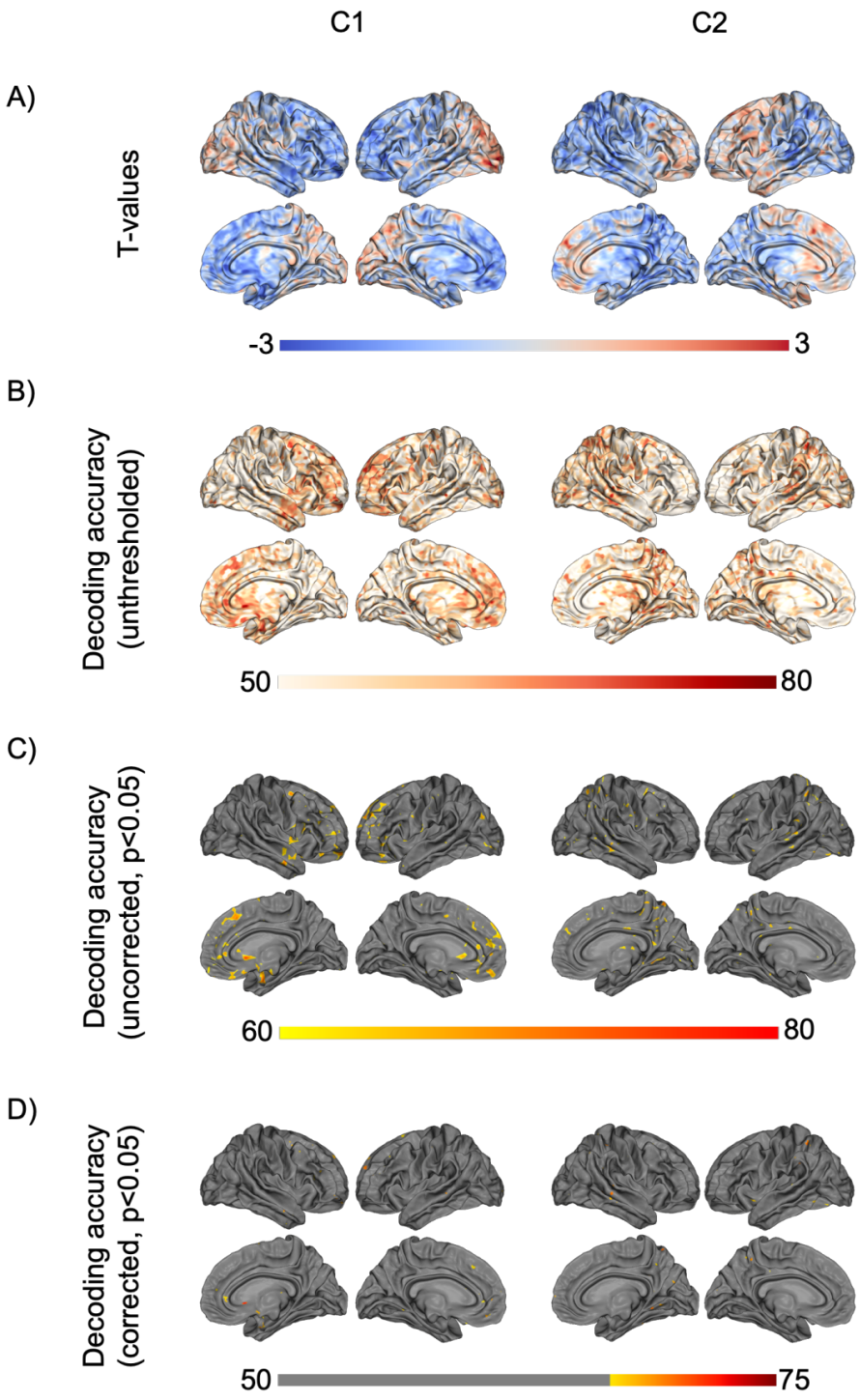


FIGURE 17: GROUP DIFFERENCES AND MACHINE-LEARNING RESULTS

(A) shows t-values from the unpaired t-tests (non-significant), showing (controls – patients). (B) shows unthresholded DA values based on logistic regression, using C1/C2 as a single feature. (C) shows the same DA values, thresholded at $p<0.05$. (D) shows the DA values corrected for multiple comparisons using maximum statistics ($p<0.05$), thresholded at the chance level of 70%. P-leader p=2 was used. DA= decoding accuracy.

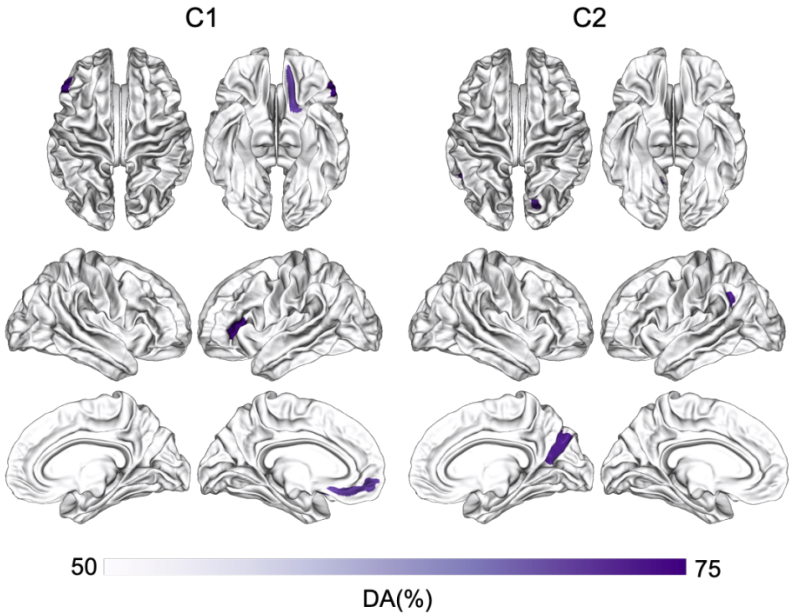


FIGURE 18: ROI-BASED CLASSIFICATION OF SZ AND CONTROLS USING C1 AND C2
Machine-learning classification of SZ patients and healthy controls using logistic regression and the features of C1 or C2 at the ROI-level. The ROI analysis was based on the Destrieux Atlas, $p<0.05$, corrected for multiple comparisons. DA=decoding accuracy, SZ=schizophrenia.

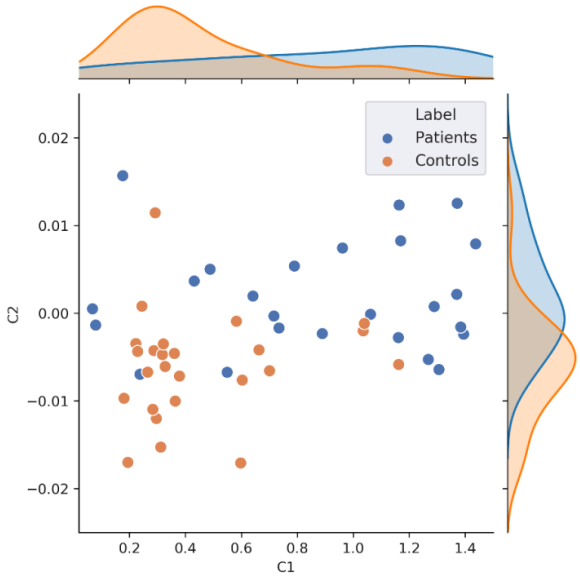


FIGURE 19: SCATTER PLOT VISUALIZATION OF INDIVIDUAL C1 AND C2 VALUES
This figure shows individual C1 and C2 values, averaged across all the nodes that showed statistically significant patient vs controls decoding (n=50). This scatter plot illustrates that patients exhibit overall higher self-similarity (higher C1) and less multifractality (higher, less negative, C2).

4.3.2 Correlations between scale-free properties and clinical information

The investigation of potential correlations between C1/C2 and clinical information resulted in a number of interesting results. Specifically, the correlations between C1 values and patients' SANS scores (maximum $r=0.78$, $p<0.05$) in the left inferior frontal gyrus and sulcus (Figure 20a), and between C2 values and patients' SAPS scores (maximum $r=0.78$, $p<0.05$) in the circular sulcus of the insula (Figure 20b) were statistically significant. In addition, the relationship between C1 and medication dosage yielded a statistically significant positive correlation (maximum $r=0.79$, $p<0.05$, after correcting across all nodes). Figures 20c and 21c illustrate that patients with higher medication dosage exhibited higher C1 values. This was especially significant in the superior frontal gyri, the right middle temporal gyrus, left mid-anterior cingulate gyrus and left inferior temporal sulcus (see Figure 20c). The positive correlations in these analyses are shown in the scatter plots in Figures 21a-c. These plots depict the relationship between individually-averaged C1 and C2 values (based on the significant nodes), and patients' symptom severity and medication dosages. To further clarify the C1 x SANS correlational results, a Pearson correlation was conducted between SANS scores and medication dosage, revealing a low-to-moderate correlation coefficient. The r2 of the regression model suggested that this relationship explained 27-40% of the data, meaning that the correlation of C1 x SANS was only partially mediated by medication.

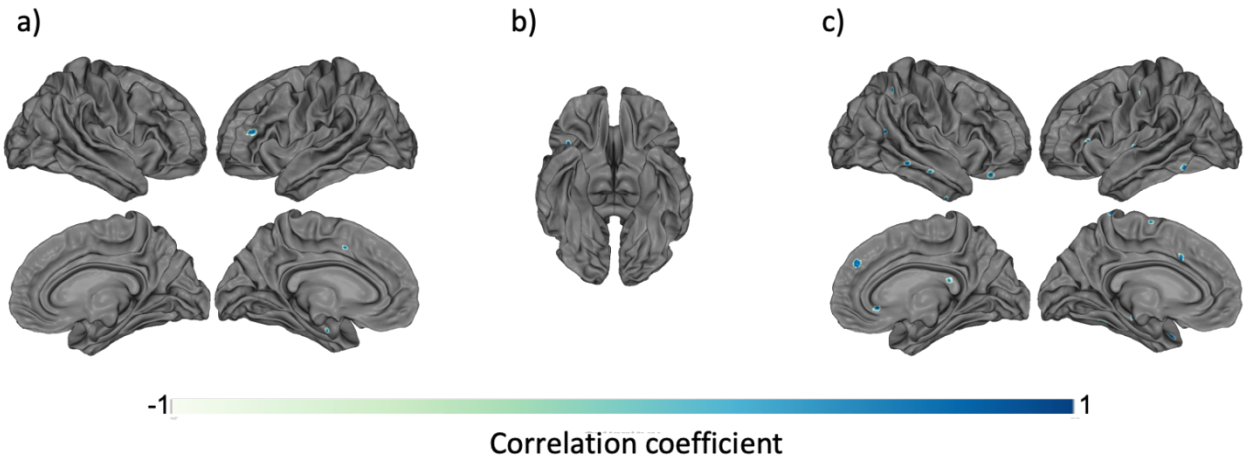


FIGURE 20: CORRELATIONAL RESULTS BETWEEN C1 AND C2 VALUES AND PATIENTS' CLINICAL INFORMATION

Pearson correlation results between patients' (A) C1 values and negative symptom scores on the SANS ($p<0.05$), (B) C2 values and positive symptom scores on the SAPS ($p<0.05$), and (C) C1 values and medication dosages (olanzapine equivalent in mg), $p<0.05$.

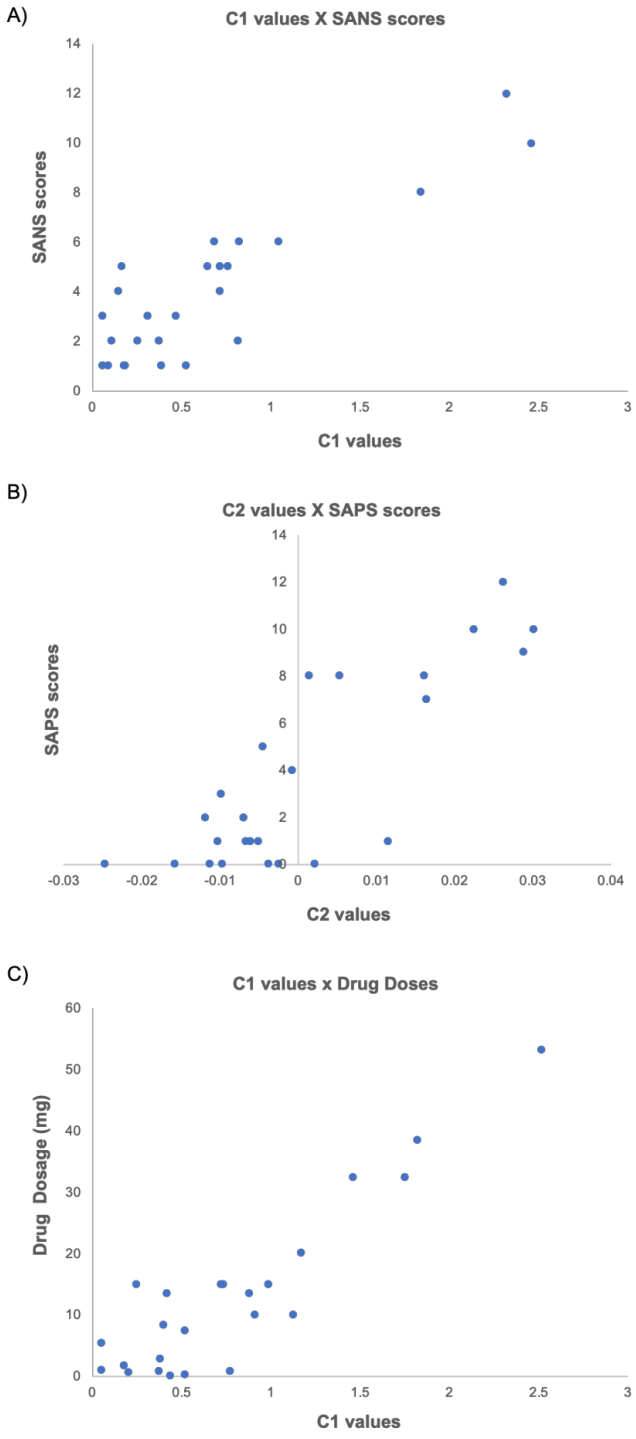


FIGURE 21: SCATTER PLOTS SHOWING THE POSITIVE CORRELATIONS BETWEEN C1/C2 VALUES AND CLINICAL INFORMATION

These scatter plots depict correlations ($p<0.05$) between individually averaged C1 and C2 values and subjects' clinical information. The averaging of C1 and C2 values was over significant nodes. (A) Shows the correlation between C1 values and patients' SANS scores, (B) shows the correlation between C2 values and SAPS scores, and (C) shows the correlation between C1 values and patients medication dosage (olanzapine equivalent in mg).

4.4. Discussion

The central goal of this study was to examine and characterize criticality features in the baseline neural dynamics of schizophrenia. To do so, we evaluated the first two log-cumulants of the Wavelet p-Leader and Bootstrap based MultiFractal (WLBMF) analysis on the resting-state neuromagnetic signals of chronic SZ patients and healthy controls. This allowed us to determine the values of C1 (reflective of self-similarity) and C2 (reflective of multifractality) on the linear, scale-free portion of participants' arrhythmic MEG signal in source-space. In brief, our findings partially supported our initial hypotheses about self-similarity and multifractality changes in SZ, whilst also revealing unexpected alterations in criticality.

Specifically, the findings of this study show that there are clear opposite gradients in the values of C1 and C2, along the rostro-caudal axis. A progression from low to high values of C1 were observed from anterior to posterior poles (i.e., frontal to occipital lobes), while C2 values showed the reverse progression. For both of these metrics, the gradient was less clear in SZ patients than in healthy controls. The t-values of the unpaired t-tests showed that patients had higher C1 values in the fronto-temporal area, and lower C1 values in the parieto-occipital areas compared to controls. In contrast, patients appeared to have higher C2 values in the temporal, parietal and occipital areas than controls. Conventional t-test statistics failed to reach significance after multiple comparisons correction. However, a machine-learning approach based on logistic regression yielded statistically significant decoding (up to 77%) of patients and controls in a number of brain regions. Indeed, SZ patients and controls were categorized using C1 values in the anterior part of the cingulate gyrus (ACC), the left inferior gyrus, and the mid and superior frontal gyri, among other brain regions. Meanwhile, using C2 as a feature, we were able to statistically significantly classify patients and controls in the right temporal gyrus, precuneus, and occipital gyrus, among other brain regions.

In terms of the first log-cumulant, patients had a range of C1 values of [0.07,1.44] in significant regions. In controls, this range was of [0.18,1.16]. Typically C1 (and thus H) values would be expected to be between 0 and 1 (where $0 < C1 < 0.5$ implies negatively autocorrelated signal, C1

= 0.5 implies uncorrelated signal, and 0.5 < C1 < 1 implies positively autocorrelated signal), although values above 1 have been observed within the theory of *generalized processes and tempered distributions* (Samoradnitsky and Taqqu, 1994). In terms of the second log-cumulant, patients had a range of C2 values of [-0.01,0.015] in significant brain regions, while controls had a range of [-0.02, 0.011]. These values fall within the same ranges reported by previous researchers (e.g., (Zilber, 2014). As a reminder, higher C1 values are indicative of more self-similarity and memory in the signal, while lower (more negative) C2 values are indicative of more complexity in the form of multifractality. From our results, we infer that SZ patients exhibited more self-similar neural dynamics than healthy controls, and thus more regularity in the frontal and temporal brain areas. In addition, patients had fewer singularities (less diverse h) in the parietal and occipital brain regions, compared to healthy controls whose neural signals were more multifractal.

Further investigation of this analysis revealed that a subportion of participants (predominantly patients) had some positive C2 values. Theoretically, only [C2 < 0] (multifractal signals) or [C2 = 0] (monofractal signals) are expected. Observing positive C2 values implies that the multifractal formalism could not properly model the neuromagnetic data recorded in these patients. So, what does this tell us about the success of the classifier in using C2 to distinguish between patients and controls? The simplest explanation is that individuals with more negative C2 (stronger multifractal properties) were identified as healthy, whereas individuals with C2 values closer to zero (monofractal), or even higher than zero (neither multifractal no monfractal), were classified as patients. As a side note, we found that using an alternate p-leader of p=4 improved C2 values, and the classifier reaffirmed the diminished multifractality characteristics of patients' resting neuromagnetic signal. Taken together, we observe clear rostro-caudal gradients of ascending self-similarity and multifractality across both participant groups, albeit more clearly in controls. The reduced multifractality and increased self-similarity might reflect a certain rigidity in the temporal dynamics of SZ patients' neural activity.

Our findings are consistent with recent publications that have characterized complexity in SZ in the same regions in which we observed alteration in the log-cumulants C1 and C2 (i.e., precuneus, inferior frontal gyrus and temporal gyrus, (e.g., Lee et al., 2020)). Interestingly, a recent resting-state MEG-based study of SZ patients by La Rocca et al. (2018) also found a gradient in C1 values

along the longitudinal axis; however, in contrast to our own finding of an ascending anterior-posterior gradient, they instead found an opposite, descending anterior-posterior gradient (La Rocca et al., 2018). Of note, there are some methodological differences between our studies, such as the choice of scale (j1 and j2) for the linear portion of the PSD. Differences could also be due to age differences. Indeed, the authors reported the mean age of their participants to be 22 years old, while our group's mean age was of 44 years old. In the complexity literature, it has been often reported that the properties of scale-free dynamics change with age (e.g., Fernández et al., 2011; Churchill et al., 2016), and so it is possible that there is a reversal of the self-similarity gradient with age. More work is needed to elucidate this.

Positive correlations were observed between the metrics of self-similarity and multifractality and patients' clinical information. In particular, we observed an increase in C1 values in patients with increasing severity of scores on the negative symptoms scale (SANS) in the inferior frontal gyrus, as well as with patient's medication dosage, the latter of which was especially strong (r=0.79). The left frontal gyrus plays an important role in cognitive functioning (Swick et al., 2008) and language (Klaus and Hartwigsen, 2019). At the structural level, cortical thinning has been observed in the inferior frontal gyrus in SZ patients compared to healthy controls, which correlated with cognitive dysfunction (Kuperberg et al., 2003; Oertel-Knöchel et al., 2013). Correlation between inferior frontal gyrus volume and negative symptoms in SZ patients have been previously observed, but not in their non-affected siblings (Harms et al., 2010). At the functional level, higher cluster coefficients have been observed in the left inferior frontal compared to bipolar patients or controls (Kim et al., 2020), as well as weaker connectivity within the language network (Jeong et al., 2009). In addition to the reported structural alterations in this language processing center, the reduction in the temporal flexibility and enhanced regularity in the signal might explain why patients' have poorer speech understanding, such as difficulty detecting metaphors, sarcasm or jokes (Rossetti et al., 2018). A correlational trend was also observed between multifractality and patients' scores on the positive symptom scale (SAPS) in the circular sulcus of the insula. In past studies, negative correlations have been observed between reduced grey matter volume of the insula and SZ patients' positive symptoms (Wylie and Tregellas, 2010; Cascella et al., 2011). It is interesting to note that self-similarity and multifractality were oppositely (and perhaps complementarily) correlated with symptom severity scores.

Taking into account the correlational findings, it is not surprising that, in our dataset of chronic and medicated patients, antipsychotic medication dosage was related to symptom severity, which itself was related to scale-free neural properties. Psychiatrists typically increase pharmaceutical dosage, gradually and as needed, to help manage symptoms. Sometimes, certain drug combinations that help manage positive symptoms (hallucinations, delusions) can worsen negative symptoms (Schooler, 1994; Goff et al., 1996). Evidence from other studies (Koukkou et al., 1993; Saito et al., 1998; Raghavendra et al., 2009) suggests that drug-naïve and first-episode patients may display a different pattern of criticality, thus the generalizability of our results is limited to other medicated, chronic SZ patients.

Another parallel can be drawn between this study's results and findings from DFA analyses. The log-cumulants (C1 and C2) derived from WLBMF analysis using a p-leader of p=2, as was used in the present study, are similar to scaling exponents obtained using DFA (Leonarduzzi et al., 2016), in that they both reflect temporal autocorrelations. In one of our recent publications, we computed DFA exponents on oscillatory envelopes in this same dataset of SZ patients and healthy controls (Alamian et al., 2020). The scale used for the computation of the log-cumulants (j1,2: 0.4-3.5 Hz) overlaps with the delta oscillatory band (0.5-3.5Hz). Comparing delta DFA exponents and C1 between the studies reveals a good agreement: DFA exponents were reduced in patients compared to controls in the occipital and parietal lobes and increased values in the prefrontal and temporal lobes, similar to the C1 topology. The overlap was remarkably good considering that DFA was computed on band-limited rhythmic brain signal, while the log-cumulants of the singularity spectrum were computed on the arrhythmic raw brain signal. This comparison shows that while DFA is an adequate measure of the self-similarity aspect of criticality, it does not however provide any information on the multifractality of a signal, as does the second log-cumulant, C2. In this respect, they capture different properties of the neural signal, and should be treated as such.

Criticality in the brain likely informs on the spatiotemporal organization and functioning of neural networks at the micro- and macroscopic levels (Hesse and Gross, 2014; Cocchi et al., 2017). While the origins of criticality are still debated, many agree that scale-free neural fluctuations are the

signature of a brain in a state of criticality. A right balance of scale invariant properties (self-similarity, multifractality) is thought to be needed to adapt and respond to ever changing environments (Linkenkaer-Hansen et al., 2001b; Plenz and Chialvo, 2009; Beggs and Timme, 2012; Palva et al., 2013b; Shew and Plenz, 2013). Consequently, we propose that a change in this equilibrium could disrupt optimal brain functioning. When self-similarity is strong in a signal, as in the brain signals of our SZ cohort, the signal's temporal autocorrelation decays slowly, such that signal memory lasts a long time. While still the subject of debate, it has been proposed that this enhanced temporal persistence (or redundancy) may make the brain less efficient in information processing (Zilber et al., 2013). Lower levels of self-similarity in signals, as in those of our healthy controls, are thought to reflect enhanced neural excitability and more efficient processing (He, 2011, 2014; Zilber et al., 2013). Interpretations of multifractality are still unclear, but it appears that a richer repertoire of singularities (multifractality > monofractality) suggests more variability and flexibility in the neural signal (Beggs and Timme, 2012), and thus in behaviour. In our dataset, patients exhibited reduced multifractality in certain areas, thus suggesting a decrease in complexity and flexibility in their resting neuromagnetic signal. The observed alterations in these criticality metrics in SZ could explain the long, sustained nature of patients' positive symptoms (delusions, hallucinations) and their difficulty in breaking away from them.

4.5 Conclusion

The overarching scale invariance of brain activity is thought to be a useful indicator of its organization across both temporal and anatomical scales (Werner, 2007; Zilber, 2014). Indeed, many have suggested that biological systems optimally process, adapt to and communicate information over long neural distances when in a state of criticality. This critical state involves a balance between regularity (structure) and flexibility (variability, local fluctuations). Disruption of this equilibrium may reduce the efficiency with which the system responds to changes in the environment. In this study, we applied WLBMF analysis to resting MEG signals and observed clear deviations in both the self-similarity and multifractality of these signals in chronic SZ patients compared to healthy controls. These changes in the state of criticality of patients lend further support to the theory of dysconnectivity in SZ from the perspective of temporal dynamics, as it

characterizes a different way in which information interruption occurs in patients. This study also demonstrated that alterations in neural criticality can be used to accurately differentiate between chronic SZ patients and controls. We expect that these findings will fuel the search for strong biomarkers in SZ, borrowing a new, largely uncharted path.

Chapter 5: Unraveling spectral changes with resting-state MEG in Schizophrenia: eyes open, closed or both ?

Abstract

Resting-state neuroimaging studies have been on the rise over the past couple of decades. These paradigms have unveiled important information about the intrinsic neural organization – and disorganization - of the brain in both healthy and clinical populations. In schizophrenia, magnetoencephalography (MEG) resting-studies have revealed key neural alterations that correlate with patients' symptoms. While two types of resting-state conditions, eyes-open (EO) and eyes-closed (EC), are used interchangeably in MEG resting-state experiments, EO and EC conditions are in fact associated with different electrophysiological patterns. Some evidence suggests that the relative difference in spectral amplitude between EO and EC resting-state data may provide insights into the ability of the brain to reorganize and readily adapt to incoming, internal or external, stimuli. Interestingly, schizophrenia patients show abnormalities in their interaction with the environment and ability to adapt to changing states. The aim of this study was to examine which resting-state feature, EO, EC or their relative difference (EO-EC/EO), would best serve as a marker for schizophrenia. We hypothesized that the relative difference in spectral amplitude between EO and EC might capture unique properties of resting neural dynamics that cannot be measured through EC or EO only. To do so, EO and EC resting-state MEG conditions were recorded in chronic schizophrenia patients and matching controls, and instantaneous amplitude was computed in source-space in the delta, theta, alpha, beta and gamma frequency bands. In each frequency band, we computed spectral amplitude for EC and EO, as well as the Relative difference in amplitude between Eyes Closed and Open (RECO) in MEG source space. Support-vector machine was used to classify schizophrenia patients and controls, with a 10-fold cross-validation scheme to determine the predictive power of these three features. Supervised machine-learning algorithms successfully categorized patients and controls with a decoding accuracy of 88% based on EO gamma-band amplitude, and a decoding accuracy of 84% based on differences in RECO in the alpha and beta-band. These results confirm the prominent role of gamma-band alterations in the neurophysiology of schizophrenia, and show that alpha and beta-

band RECO could provide a more robust marker of pathology than EC or EO in certain cases. Future studies should consider systematically acquiring both EC and EO resting-state conditions, and using multifeature classification techniques to improve the search of a biomarker in schizophrenia.

5.1 Introduction

Over the past two decades, it has become clear that improving our understanding of the intrinsic neural organization of the brain is an important step in better grasping the intricacies of the healthy, aging and diseased brains (Greicius, 2008; Lowe, 2010). With that, interests in resting-state neuroimaging studies have been on the rise, both in healthy (Beckmann et al., 2005; Damoiseaux et al., 2006; Mantini et al., 2007; van den Heuvel and Hulshoff Pol, 2010b; Snyder and Raichle, 2012) and psychiatric populations (Mulders et al., 2015; Alamian et al., 2017b, 2017a; Newson and Thiagarajan, 2019). Indeed, resting-state studies have revealed key insights into the pathophysiology of psychiatric illnesses. Specifically, the complex field of schizophrenia has benefited greatly from the characterization of the baseline neural properties of patients. For instance, increases in slow oscillations (delta, theta) (Boutros et al., 2008; Venables et al., 2009; Kam et al., 2013; Narayanan et al., 2014; Di Lorenzo et al., 2015), and increases in fast oscillations (gamma) have been reported in patients (Venables et al., 2009; Gandal et al., 2012; Andreou et al., 2015; Di Lorenzo et al., 2015; White and Siegel, 2016), which appear to correlate with their symptom severity (Sperling et al., 2002; Fehr et al., 2003). Graph theory studies have revealed resting-state changes in the efficiency of patients' neural networks that correlate with their clinical profiles (e.g., illness duration, symptom severity) (Liu et al., 2008; Guye et al., 2010). Functional magnetic resonance imaging (fMRI) studies and electrophysiological studies have also provided evidence for the leading theory of spatiotemporal dysconnectivity in schizophrenia: altered connectivity patterns within the prefrontal cortex (Hinkley et al., 2011; Karbasforoushan and Woodward, 2012; Woodward et al., 2012; Robinson and Mandell, 2015; Giraldo-Chica and Woodward, 2016), decreased connectivity between temporal and frontal lobes (Friston, 1996; Higashima et al., 2007), and increased connectivity between occipital and central brain regions (Wada et al., 1998; Karbasforoushan and Woodward, 2012), and between thalamus and sensorimotor regions (Karbasforoushan and Woodward, 2012; Wang et al., 2015b; Giraldo-Chica

and Woodward, 2016). Overall, it is evident that resting states studies have improved our understanding of the neurophysiological mechanisms of this pathology. A comprehensive review of resting electrophysiological alterations in schizophrenia can be found in our recent publication (Alamian et al., 2017b).

5.1.1 Resting state studies across neuroimaging methods

Three resting-state paradigms are typically used in neuroimaging studies: recordings with participants having their (1) eyes-closed, (2) eyes-open or (3) eyes open and fixating cross-hairs. In fMRI studies, the most commonly used method to tap into this baseline neuronal state is with an eyes-open condition, where participants are asked to fixate on cross-hairs (or "+" sign), while they let their mind wander (Patriat et al., 2013). In electrophysiological resting-state studies, eyes-open (EO) and eyes-closed (EC) paradigms are used fairly evenly. However, there is no gold standard for the parameters of these resting-state recordings (van Diessen et al., 2015b; Alamian et al., 2017b), and variable durations have been used (e.g., 3 min to 10 min); recording duration can severely affect the reproducibility of magnetoencephalography (MEG) findings (Liuzzi et al., 2016). Other factors that can substantially impact test-retest reliability of resting-state data is the level of compliance of patient populations during recordings (e.g., head movement, sleepiness/drowsiness), and age (Song et al., 2012). Despite these limitations, EO and EC conditions have proven to be useful in the search of novel biomarkers in psychopathologies.

5.1.2 Relative difference in eyes-open and eyes-closed conditions

Instead of focusing on either EO or EC resting-state data, a number of studies have examined what the change between EO and EC paradigms can reveal about brain dynamics in healthy and clinical populations. A substantial body of evidence suggests that the dynamics of neural networks change when switching between EO and EC resting states (Bosboom et al., 2006; Barry et al., 2007; Bianciardi et al., 2009; Tan et al., 2013; Jin et al., 2014; Wong et al., 2016; Alamian et al., 2017b, 2017a; Gómez-Ramírez et al., 2017; Wei et al., 2018; Agcaoglu et al., 2019; Candelaria-Cook et al., 2020; Ikeda et al., 2020). More specifically, absolute MEG (electrophysiological) power across various frequency bands has been shown to be higher during EC condition than EO conditions in

both healthy controls (Heister et al., 2013) and patient groups including Alzheimer disease (Ikeda et al., 2020) and Parkinson's disease (Bosboom et al., 2006). Comparable results are seen in EEG data (Barry et al., 2007), with the switch between EC and EO bringing about topological changes in delta, theta and beta power in healthy controls, as well as an overall magnitude reduction in the alpha-band. Interestingly, the relative amplitude difference between resting conditions has been found to be bigger in certain clinical populations than in controls, such as in Alzheimer patients (Ikeda et al., 2020) for the theta, alpha and beta bands, across different brain regions. Conversely, MEG alpha-band reactivity (change from EC to EO) appears to be reduced in schizophrenia patients compared to controls (Candelaria-Cook et al., 2020).

5.1.3 Rational

The modulation of neural dynamics between conditions of EO and EC might reveal something more informative about brain functioning than the simple characterization of ongoing spontaneous brain activity (Ikeda et al., 2020). In fact, it has been suggested that the switch from EC to EO allows neural networks to reorganize and readily adapt to incoming stimuli from the surrounding environment (Jin et al., 2014). Thus, the comparison of brain activity recorded in these two resting-state paradigms, using the Relative difference in spectral amplitude between Eyes Closed and Open (RECO), could provide new insights on the "reactivity" of resting neural dynamics. This might be particularly relevant in schizophrenia patients, who exhibit atypical interactions with their environment (Jin et al., 2014).

5.1.4 Goal of the study

The objective of this study was to examine how resting MEG amplitudes differ between EC and EO conditions in healthy controls and schizophrenia patients, and compare the predictive power of (a) spectral amplitude during EO, (b) spectral amplitude during EC and (c) the relative difference between the two (RECO) in discriminating between these two groups. We hypothesized that the feature of RECO might capture properties of the resting neural functioning of patients that would otherwise go unnoticed if we used EO or EC conditions alone.

5.2 Materials and methods

Data collection took place at Cardiff University, Wales, U.K., while analyses were conducted at the University of Montreal, Q.C., Canada. Ethical approvals were obtained from the U.K.'s National Health Service and the Cardiff University School of Psychology ethics boards (EC.12.07.03.3164). Approval was also obtained from the ethics committee at the University of Montréal (CERAS-2018-19-069-D).

5.2.1 Participants

Behavioural, demographic and neuroimaging data was collected from 50 participants: 25 chronic schizophrenia patients (mean age = 44.96 ± 8.55, 8 females) and 25 healthy controls (mean age = 44.04 ± 9.20, 8 females). The aims of this study rested on incorporating EO and EC resting-state signals of each participant simultaneously, thus we had to exclude data from two control participants, for whom we were missing one of their two resting-state conditions. Therefore, the following analyses included data from a total of 48 participants: 23 healthy controls and 25 chronic schizophrenia patients.

Age, gender, depression score on the Beck Depression Inventory – II (BDI-II (Beck et al., 1996)) and mania score on the Altman Self-Rating Mania Scale (Altman et al., 1997) were collected for each participant. Moreover, schizophrenia patients' symptoms severity score on the Scale of the Assessment of Positive Symptoms (SAPS) and the Scale of the Assessment of Negative Symptoms (SANS) (Kay et al., 1987), as well as information on their medication dosages (standardized using olanzapine equivalents (Gardner et al., 2010)), were obtained. Patients and controls did not differ on any of the reported information, except for BDI-II scores, where patients showed mild depressive symptoms, while controls did not. Overall, patients were fairly asymptomatic during data collection. Full description of participants' recruitment, inclusion/exclusion criteria, and demographic and clinical information can be found in Chapter 3 (Alamian et al., 2020).

5.2.2 MEG experimental design, data preprocessing and source-reconstruction

An anatomical T1-MRI as well as two resting-state MEG scans (lasting five-minutes in each EO and EC conditions) were recorded for each participant. The MEG scanner was a 275-channel CTF machine, located in Cardiff, U.K. This multimodal approach allowed for proper source-reconstruction and source-estimation of each subjects' MEG time-series. Reference electrodes were used to record ocular movements and other potential artifacts (Messaritaki et al., 2017).

The preprocessing and source-reconstruction analyses were conducted with the open-source python pipeline, NeuroPycon (Meunier et al., 2020). The raw MEG time-series were first recorded at a sampling frequency of 1200 Hz, then downsampled offline to 600Hz, and filtered between 0.1-150 Hz. Ocular, muscle and cardiac artefacts were removed using independent component analysis (Hyvarinen, 1999; Gramfort et al., 2013). Each participants' anatomical T1 was segmented with FreeSurfer (Fischl, 2012), implemented in NeuroPycon. Individual source spaces were then morphed and projected onto the standardized *fsaverage* (Greve et al., 2013), resulting in a source-space consisting of 8196 dipoles for each subject. Next, the lead field matrix and the inverse solution were computed with the MNE-python single layer model boundary element method (Gramfort et al., 2013) and weighted minimum norm estimate (Dale and Sereno, 1993; Hamalainen et al., 1993; Hämäläinen and Ilmoniemi, 1994; Hincapié et al., 2016), respectively (Hyvarinen, 1999; Gramfort et al., 2013).

5.2.3 Measuring spectral amplitude and reactivity

Instantaneous amplitude of the MEG signal was computed at each of the 8196 nodes, for each participant, in the delta (0.5-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-29 Hz), and gamma (30-60 Hz) frequency bands, by filtering the raw signal using a finite impulse response filter and computing the Hilbert transform (Le Van Quyen et al., 2001; Foster et al., 2016). This was done in both the EO and EC conditions. Next, in each frequency band, relative difference in amplitude (RECO), was computed for each node : $RECO(f) = [(EO(f) - EC(f))/EO(f)]$, where f is the frequency band.

5.2.4 Machine-learning analyses

MEG signal classification was conducted using a support vector machine model and a stratified 10-fold cross-validation scheme to evaluate the discriminative power of relative spectral amplitude differences (i.e., RECO, in each frequency band) in classifying schizophrenia patients and controls, in comparison to EO or EC. The feature of RECO at each of the 8196 nodes was first split into ten folds, respecting the balance between patients and controls. Next, SVM was trained on data from nine of the ten folds, and tested on the remaining fold. Then, the performance of the classifier was assessed using a decoding accuracy (DA), by evaluating the percentage of participants that were correctly classified across the total number of participants in the test set. This procedure was repeated iteratively, such that all ten folds were used as test sets. The average DA at each node was then used as the performance metric of the classification of the two groups. Lastly, permutation tests (Combrisson and Jerbi, 2015) and maximum statistics were used to evaluate the statistical significance of the reported DA (Nichols and Holmes, 2001; Pantazis et al., 2005), and to control for the multiple comparisons across the 8196 nodes. This classification procedure was repeated using EO and EC as features in order to compare their ability to discriminate between patients and controls, with respect to RECO.

5.3 Results

5.3.1 Relative amplitude difference between EC and EO in schizophrenia and controls

Figure 22 shows that both, topological and magnitude, differences in RECO can be observed within and between the two subject groups. Large reductions in delta-band amplitude were found in controls in the inferior frontal gyri, temporal, parietal and occipital lobes. Patients showed comparable reductions in delta-band reactivity in the occipital lobes, as well as an increase in RECO in the frontal lobes. Similar reductions were seen in the theta-band amplitudes of controls, along with important increases in RECO in the left frontal lobe. The theta-band changes in patients were more bilateral and subdued in magnitude compared to controls: moderate amplitude reductions in the parietal and occipital lobes and slight increases in the frontal lobes. Both subject groups displayed similar reductions in alpha-band RECO across most of the cortex, and beta-band

reductions of RECO in the occipital lobe and increases in the frontal lobe, with varying intensities. Topological differences in RECO were observed in the gamma-band, with patients showing an overall increase in amplitude, particularly in the frontal and temporal lobes. Meanwhile, controls showed an increase in gamma-band amplitude in fronto-temporal regions, and a decrease in the inferior frontal and cingulate gyri.

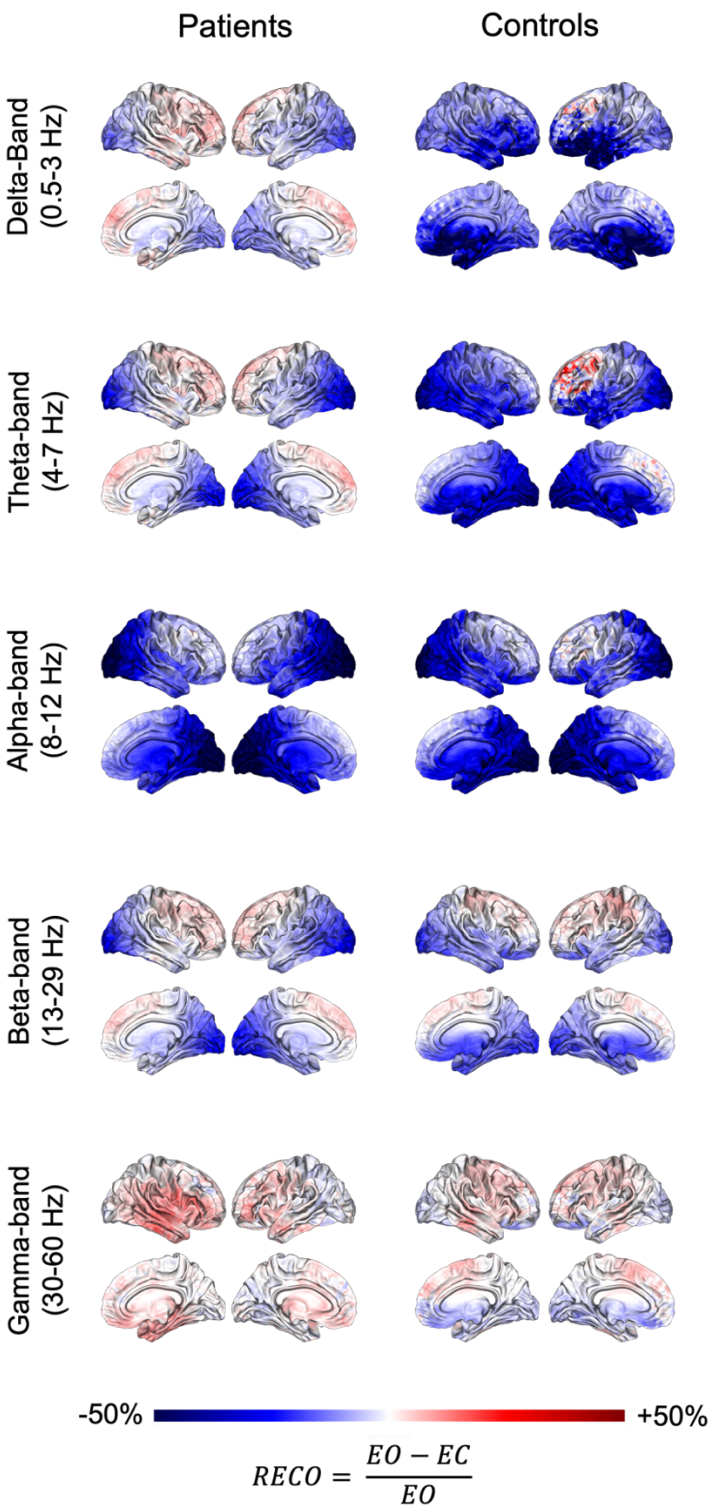


FIGURE 22: RELATIVE DIFFERENCE IN AMPLITUDE BETWEEN EO AND EC
This figure shows RECO in each subject group, for each frequency band. Blues indicate a drop in amplitude magnitude in the EO condition, while reds indicate an increase in amplitude magnitude in the EO condition. EO= eyes-open, EC=eyes-closed, RECO = Relative amplitude difference between Eyes Closed and Open.

5.3.2 Comparison between predictive power of EO, EC and RECO amplitude

Machine-learning classification of schizophrenia patients and healthy controls were conducted in three conditions: EO, EC and RECO. Using supervised machine-learning, group differences in RECO statistically significantly classified patients and controls with up to 84% accuracy ($p<0.05$). The strongest decoding took place in the alpha and beta frequency bands. Specifically, in the alpha-band, SVM categorized patients and controls successfully in the left superior temporal gyrus and postcentral gyrus, and in the right parahippocampal gyrus (Figure 23). In the beta-band, groups were significantly classified in the left middle occipital gyrus, angular gyrus and precuneus, and in the right posterior-central cingulate gyrus and superior frontal gyrus. No significant classification was found in the theta band.

Figure 23 also shows the classification results obtained when using spectral amplitude in EO and EC resting-state conditions. Spectral amplitudes of all frequency bands yielded significant categorization of patients and controls using EO as a feature, the most prominent of which was in the gamma-band. In fact, gamma-amplitude in the left straight gyrus allowed for an 88% decoding accuracy ($p<0.05$) of controls and patients (Table 6). Gamma-amplitude yielded significant DA in the left temporal pole, right precuneus and parahippocampal and subcallosal gyri. Additionally, groups were significantly classified based on EO theta and delta amplitudes in the left parieto-occipital sulcus and right temporal pole. Successful categorization was also observed in the left postcentral gyrus and sulcus and marginal branch of the cingulate sulcus based on alpha-band amplitude, and in the left angular and supramarginal gyri, right superior parietal lobule and precuneus and parahippocampal gyri based on EO beta-band amplitude. Using EC as a feature of the classification model, peak DA was observed in the gamma-band amplitude in the left temporal pole (84%, $p<0.05$, maximum statistics correction). Significant classification of patients and control was also seen in the subcallosal gyri, bilaterally. DA values in the EC condition were otherwise not as high in the other frequency bands, as they were in EO (Table 6).

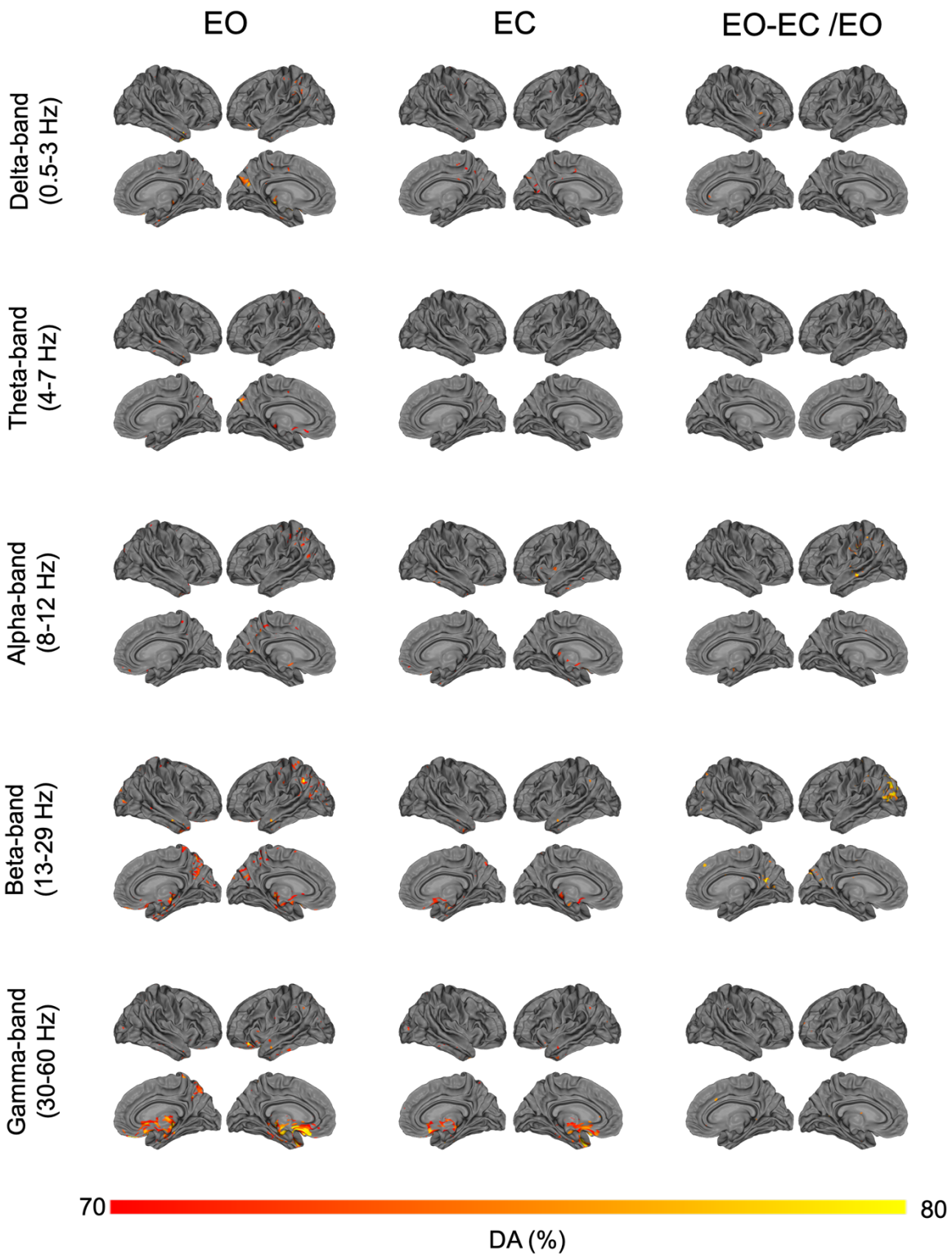


FIGURE 23: CLASSIFICATION RESULTS OF THE MACHINE-LEARNING CLASSIFICATION BASED ON RECO

Summary of statistically significant support-vector-machine results, in each frequency band, using RECO at each node as a feature ($p<0.05$, corrected). RECO= Relative difference in Eyes-Closed and eyes-Open.

TABLE 6: MAXIMUM DECODING ACCURACY VALUES ACROSS RESTING STATE CONDITIONS

Frequency-band	Max DA for EO (%)	Max DA for EC (%)	Max DA for RECO (%)
delta	84	79	77
theta	78	74	76
alpha	77	82	84
beta	83	77	84
gamma	88	84	78

Table 6 - caption: Peak DA value (%) are summarized in each condition and each frequency band. DA = decoding accuracy, EC = eyes-closed, EO = eyes-open, RECO = relative difference in amplitude between eyes-closed and open.

5.4 Discussion

Studies of the relative difference in spectral amplitude between EC and EO resting-state conditions (RECO) in psychiatry are scarce. This study was the first to investigate the predictive power of amplitude across resting-state conditions in schizophrenia. Specifically, we examined how EO, EC and RECO differed in their classification capabilities of chronic schizophrenia patients and healthy controls. To assess their predictive power, we used a supervised machine-learning framework.

Our findings echo those of previous studies, who have found neural changes between the EO and EC resting state paradigms in pathologies (Bosboom et al., 2006; Alamian et al., 2017a, 2017b; Candelaria-Cook et al., 2020; Ikeda et al., 2020), and healthy controls (Barry et al., 2007; Bianciardi et al., 2009; Jin et al., 2011, 2014; Tan et al., 2013; Wong et al., 2016; Gómez-Ramírez et al., 2017; Wei et al., 2018; Agcaoglu et al., 2019). Relative MEG amplitude was drastically reduced in EO compared to EC in the occipital and temporoparietal lobes and the cingulate gyri in healthy controls. Similar findings were observed in patients, albeit to a lesser extent in the theta and delta frequency bands. Topological differences in RECO were also found

in patients in the theta, delta and gamma frequency bands. Meanwhile, in the alpha and beta bands, the observed group differences in RECO were mainly of magnitude in nature (i.e. size of RECO) and not topographic distribution of RECO across the brain. Unlike the MEG findings reported in (Candelaria-Cook et al., 2020), we found a slightly bigger alpha RECO in schizophrenia patients than in controls. These opposing results are surprising, but might be due to the small sample size (13 patients and 13 controls) or methodological differences in the acquisition of the data in the aforementioned study (e.g., length of resting-state recordings), all of which can substantially affect replicability of results.

The machine-learning classification results revealed that gamma-band amplitude in the EO condition was the best predictor of schizophrenia. Indeed, the enhanced resting gamma-band amplitude in the left straight gyrus, temporal pole, right precuneus and subcallosal gyri were able to significantly categorize patients and controls with a maximum DA of 88%. This finding is in accordance with previous research which has highlighted the importance of gamma-band activity alterations in the pathophysiology of schizophrenia (Gandal et al., 2012; Uhlhaas and Singer, 2013).

Schizophrenia patients and healthy controls were successfully classified based on alpha-band and beta-band RECO with a decoding accuracy reaching 84%. This classification was higher than the decoding accuracies that were achieved with either alpha- or beta-band amplitudes in EO or EC. Indeed, the two groups were successfully categorized based on alpha-band RECO in the left superior temporal and post- central gyri, among other regions, and based on beta-band RECO in the left occipital gyrus and precuneus and the right frontal gyrus. These results showed that patients' alpha and beta-band reactivities were larger than those of controls in the aforementioned brain regions.

In keeping with previous research, the present findings support that alpha-band global reduction in power is thought to reflect changes in arousal (Wong et al., 2016), while topological changes are thought to reflect situation-based activation processes (Barry et al., 2007). In addition, changes observed in RECO are thought to relate to information processing in the brain (Tan et al., 2013), and to correlate with working memory functioning (Heister et al., 2013). These two cognitive

aspects are often deficient in chronic schizophrenia patients (Hinkley et al., 2010; Sheffield and Barch, 2016). Our results could thus suggest that schizophrenia patients are less aroused than healthy controls during EO conditions, and that their resting neural organization is less apt to adapt to incoming environmental stimuli compared to healthy controls. Although, a link between RECO and symptoms might seem obvious, additional correlational analyses (not reported here) did not yield any significant result. A larger sample size, and additional symptoms scores on cognitive functions (i.e., inhibitory functioning), might help elucidate this hypothesis. Nevertheless, more work is needed to better expand on the involvement of resting-state conditions on the intrinsic neural dynamics of psychopathologies. It would be of particular interest to evaluate the predictive power of EO and RECO paradigms in youth that might be at-risk of developing psychosis, as this could potentially serve as an easy and accessible way to detect neural abnormalities.

It should also be noted that the two, EO and EC, resting-state conditions might offer complementary, but different, baselines for psychiatry-based research studies (Agcaoglu et al., 2019). It has been proposed that EC paradigms might be best suited as a general baseline level of arousal, while EO paradigms might serve best as a baseline for occipital-lobe activity for visual tasks (Barry et al., 2005, 2007). Future resting-studies interested solely in the characterization of intrinsic neural dynamics should consider acquiring both EO and EC data, and potentially using a multifeature classification approach, combining EO, EC and RECO.

5.5 Conclusion

This study reports for the first time how brain activity in eyes-open and eyes-closed resting-state conditions, across a wide range of frequency bands, differ between chronic schizophrenia patients and healthy controls, and highlights how EO gamma-amplitude and RECO alpha/beta-amplitudes can be used to successfully categorize patients from controls. This study could provide new insights with possible implications in the future of early diagnostic measures for schizophrenia. A longitudinal study could help reveal if RECO is observed in those at-risk of developing psychosis, and measure whether it can be used as a tool to assess psychopathologies, such as schizophrenia, in a large cohort. Our findings also support previous studies that underline that different neuroimaging paradigms (i.e., EO vs EC) can reveal different patterns of resting neural dynamics.

Future studies in psychiatry might want to consider systematically acquiring both EO and EC resting-state data to improve their understanding of the baseline neural functioning of illnesses.

Chapter 6: Discussion

6.1 Summary of the objectives and findings

Despite a growing body of research, progress in understanding the neurophysiological mechanisms that underlie the symptoms of schizophrenia is relatively slow. The overall aim of this thesis was to evaluate whether the spatiotemporal structure of the resting neural signal can reveal new features of brain organization in psychiatric illnesses. Throughout the presented studies, this was achieved by combining state-of-the-art metrics of criticality, machine-learning and MEG.

Overall, we revealed alterations in the neural dynamic of schizophrenia patients at rest, in terms of self-similarity and multifractality. A general attenuation in cortical and subcortical levels of LRTCs was observed in the alpha and beta oscillatory amplitudes of patients, compared to healthy controls. Moreover, an increase in self-similarity (C1) in the frontal and temporal brain regions and a decrease in multifractality (C2) was shown in patients' parieto-occipital regions in the arrhythmic part of the neuronal signal. These findings suggest that, compared to controls, chronic schizophrenia patients had overall decreased memory (and increased variability) in alpha and beta neural oscillations. Additionally, patients had increased memory and regularity in arrhythmic, low-frequencies (0.5-3.5 Hz), in the frontotemporal brain regions, and more monofractal (fewer singularities) in parietal-occipital regions. Meanwhile, healthy controls exhibited higher overall LRTC values in the alpha and beta bands, as well as more multifractality in those same brain regions. The increased regularity in the arrhythmic signal of patients is indicative of temporal redundancy/persistence and, perhaps, of less efficient information processing. Meanwhile, the decreased fractality and complexity observed in patients could suggest less flexibility in their parietal-occipital brain areas. We propose that these findings could explain the sustained (i.e. persistent) nature of symptoms (e.g., long-lasting auditory hallucinations), and the difficulty many patients have in breaking away from them. Meanwhile, the reduced regularity and memory observed in the rhythmic part of patient's brain signal might reflect a break in communication, and difficulties for the propagation of information through oscillations, and lends support to the spatiotemporal dysconnectivity theory in schizophrenia.

We also examined whether alterations in scale-free dynamics are related to patients' symptoms. We found that there was indeed a positive correlation between self-similarity (C1) and patients' SANS (negative) scores, and between multifractality (C2) and patients' SAPS (positive) scores. The most significant correlations were between theta and delta amplitudes and SANS scores, as well as between C1 and medication dosage, replicating findings from previous researchers [low oscillatory amplitudes x SANS: (Chen et al., 2016; Fehr et al., 2003; Jandl et al., 2005; Venables et al., 2009); self-similarity x medication: (Takahashi et al., 2010; Fernández et al., 2013)]. Moreover, while (SANS x medication) showed a moderate correlation, indicating that medication was associated to symptom scores, it did not fully account for the variance observed in the correlation between C1 and SANS. The involvement of medication in alterations of neural dynamics is not surprising and has been explicitly reported in the psychiatry literature (Navari and Dazzan, n.d.; Kirsch et al., 2007; Schmidt et al., 2013; Alegre et al., 2017).

Finally, we examined whether local amplitude alterations measured across different resting-state paradigms (EO, EC or RECO – the relative difference in amplitude between EC and EO conditions) could be used as a marker for schizophrenia. The results of the classification revealed that gamma-band amplitude in the EO conditions was the best predictor of schizophrenia (88% DA), replicating previous findings that have highlighted the important role of gamma alterations in the pathophysiology of schizophrenia (Wilson et al., 2009; Uhlhaas and Singer, 2013). The study also showed that RECO was larger in the alpha and beta bands in patients than in healthy controls, such that SVM categorized patients and controls based on this feature with a significant decoding accuracy of 84%. Differences between EC and EO have been linked to changes in arousal (Wong et al., 2016), information processing (Tan et al., 2013) and cognitive functioning (Heister et al., 2013), all of which is often deficient in schizophrenia patients. Thus, alterations in RECO could be part of the aberrant neural mechanisms in this pathology.

6.2 Contribution to the field of psychiatry

The first two reviews were important from a number of perspectives. First, they clarified the terminology around connectivity analyses (ie.g., local vs long-range synchrony), which is needed to harmonize the scientific discussions across the field. Second, they updated the literature on

findings related to electrophysiological-based connectivity changes in mood disorders and schizophrenia. Third, they discussed the utility of growing MEG studies in psychiatry, as well as the methodological challenges involved in clinical research. The reviews also recommended important analytical and design considerations for future MEG studies.

Chapters 3 and 4 tapped into the underexplored field of criticality in psychiatry (Linkenkaer-Hansen et al., 2005; Nikulin et al., 2012; Moran et al., 2019; Zimmern, 2020). The first study characterized how scale-free properties of MEG oscillatory amplitude are changed in schizophrenia. It revealed that patients could be successfully classified using solely the features of alpha or beta LRTC values at the cortical and subcortical levels. Importantly, group differences in LRTCs were not confounded by factors of age, gender or amplitude magnitude. This study was the first to examine scale-free dynamics of resting neural networks in schizophrenia in deep structures, and the first to utilize machine-learning on DFA data. The second study applied the WLBMF analysis on arrhythmic schizophrenia data for the first-time. Interesting patterns of group differences in the measures of self-similarity and multifractality were observed, with a clear imbalance in these two parameters in schizophrenia patients. We also drew the first parallels between LRTCs in the delta-band and the C1 log-cumulant values. We found commonalities in the results, with enhanced values of self-similarity in the frontal and temporal brain regions and decreased values of self-similarity in the occipital lobe, compared to controls. Together, these two chapters allowed us to determine which scale-free metric is most informative on the neuropathology of schizophrenia. We found that, across scale invariant properties, DFA was the best at classifying patients and controls (84% decoding accuracy). Nevertheless, the C1 and C2 log-cumulants revealed new information on how multifractality was altered in patients. Although the domain of fractal analysis is still underdeveloped in clinical neuroscience, it has immense potential to further the scientific community's knowledge of the temporal structure and geometry of brain signals in healthy and diseased brains (He, 2014; Palva and Palva, 2018).

The final chapter addressed the question of which resting-state feature (spectral amplitude in EO, EC or the relative difference in amplitude between EC and EO) would best serve to identify biomarkers in schizophrenia. Until now, most of the literature has focused on task-based approaches to see how brain function is different during specific tasks, but this study underlined

the importance of defining and characterizing the neural functioning of patients at baseline (i.e. resting-state). Moreover, given that electrophysiological studies use EO and EC conditions interchangeably, it is important to clarify the different contributions that each resting-state paradigm can provide to the discussion of schizophrenia. Our findings highlight the need for more resting-state research in psychopathologies that incorporate both EO and EC conditions, as they each reveal unique alterations in neural dynamics that could be used as a simple and non-invasive way to identify patients in the future. Future studies should consider combining gamma-band EO and alpha/beta-band RECO changes in a multifeatured machine-learning framework to improve classification results.

Together, the studies included in this thesis identify candidate diagnostic markers that should be explored in future longitudinal studies for their potential prognostic values. Indeed, alterations in scale-free dynamics could help predict the prognosis of individuals at-risk of developing psychosis, thus becoming a powerful clinical tool. More work is needed to validate these hypotheses.

In addition to the contributions made to the clinical research community, this work has a potential impact on our understanding of the biological mechanisms of schizophrenia. When looking to identify and evaluate potential biomarkers, it is critical to assess its validity at all micro- and macroscopic levels of the pathology: from a genetic perspective to a neuroimaging and behavioural perspective. Today, over 100 genetic loci have been associated with schizophrenia, such as genes including but not limited to: glutaminergic transmission, calcium signaling and dopaminergic transmission (Ripke et al., 2014). More specifically, genes involved in the *N*-methyl-*D*-aspartate receptor (NMDAR) (Coyle, 2012; Balu, 2016), catechol-O-methyltransferase (COMT) (Egan et al., 2001; Shifman et al., 2002; Wonodi et al., 2003) and the D2 dopamine receptor (Glatt et al., 2003; Seeman, 2006) are some of the most commonly discussed genes. COMT is involved in prefrontal cortex dopamine metabolism, and COMT Val/Val polymorphism has been linked to an increased risk of psychosis, especially when combined with early-onset use of cannabis (Caspi et al., 2005). Relating this to the results of Chapter 3, it has been suggested that alterations in NMDA-receptor conductance prompts increases in the variability of the brain signal , as well as long-term decreases in the stability/correlation of the signal (Loh et al., 2007; Rolls et al., 2008), similar to

our LRTC findings (Chapter 3). However, this interpretation is limited given that the state of criticality also affect gene expression (reverse causality). A great review on the neurobiology of criticality in the brain can be found in (Cocchi et al., 2017).

6.3 Utility of machine-learning framework in psychiatry

As described in the introduction of this thesis, compared to conventional statistics, machine-learning algorithms (using single or multiple features) allow for better classification of subject groups, and for generalizability of the findings in new cohorts of patients and controls with similar characteristics. In our studies, the machine-learning framework led to significant findings in key brain regions that exhibited altered spectral amplitude or scale-free features. Interestingly, across all three original studies of this thesis, the peak magnitudes of group differences (i.e., t-value peaks) corresponded to the decoding accuracy peaks obtained with the machine-learning analyses. For both studies, the areas with the largest group differences in terms of t-values (very red or very blue) were the ones that best decoded the two subject groups with significant accuracy. Although there are different way to apply machine-learning approaches, our studies adopted a single-feature machine-learning strategy, given that the focus was on maximizing the interpretability of the results, improving the pathophysiological understanding of SZ, and benefiting from out-of-sample generalizations. The predictive models that are generated by machine-learning frameworks also permit the extrapolation of conclusions from one dataset to another. This is increasingly important given the shift towards more collaborative work, which calls for data-sharing and the leveraging of multiple data sets to increase overall sample sizes ("Big data"). Furthermore, given the heterogeneity in the clinical presentations of schizophrenia, and that symptoms arise from a mix of genetic, environmental and epigenetic factors (Van Os et al., 2008; Akbarian, 2014; Nestler et al., 2016), machine-learning approaches have immense potential in helping improve the sub-classifications of patients, and shift towards personalized treatments. This type of multifeature machine-learning strategy would however require dimensionality reduction of the feature space (e.g., through the use of Principal Component Analysis). Dimensionality reduction reduces the complexity of the data, improves computational efficiency and prevents the over-fitting of the multifeature model to the data (Kherif and Latypova, 2019; Reddy et al., 2020). While this

approach could lead to numerically higher decoding accuracies, it would also be increasingly challenging to interpret the results from an electrophysiological perspective.

Lastly, although conventional statistics and machine-learning provide complimentary information, in clinical practice, the emphasis is put on prediction abilities, rather than on hypothesis testing as is typical in conventional statistics. Indeed, the main objectives are to obtain models that minimize error when predicting the outcomes of new data (patients) based on a previously learned (or trained) relationships (Koppe et al., 2021), rather than testing hypotheses based on a *apriori* model. One way to achieve this, while leveraging the multimodal data of psychiatric patients, is through the use of unsupervised clustering techniques on resting-state data (Koutsouleris et al., 2009; Clementz et al., 2016; Uhlhaas et al., 2017), and future work is need to fully optimize these techniques (further discussed in section 6.5).

6.4 Limitations

Similar to most clinical research studies, one of the drawbacks of this thesis is that the generalizability of the findings are limited to similar clinical cohorts. Across the three studies, our sample consisted of chronic schizophrenia patients, with an average age of 44 years. Age, duration of the illness, accumulation of therapeutic drugs, and number of psychotic episodes all impact the symptomatology and neural functioning in their own ways (Lieberman et al., 1996). That said, another limitation is that information about illness duration and number of total psychotic episodes was not acquired during data collection. In retrospect, it would have been interesting to see how these two factors would affect measures of scale-invariance. Future studies should take into account these key factors when designing experiments by including them as co-variables, or by recruiting other types of control groups (e.g., a group of similarly aged patients with a shorter illness duration, or fewer episodes).

Another possible limitation is the confounding effects of residual symptoms on the interpretation of our results. Although the schizophrenia cohort had a fairly asymptomatic clinical presentation, all participants were medicated with antipsychotics, which typically manage patients' positive symptoms, but not negative or cognitive symptoms to the same extent. Indeed, our analyses show that patients had residual negative and depressive symptoms, as shown by their SANS and BDI-II

scores. These symptoms could have been heterogenous in nature and affected the findings. Failure to take into account the sub-types of negative symptoms in future studies might hinder the cumulative progress we make in the field.

Sample size was another limitation of our studies. While, our cohort of 50 subjects (25 schizophrenia patients, 25 controls) was reasonable for a neuroimaging study examining resting-state neural organizations, a larger sample size, or a different out-of-sample test group, might have improved the accuracy of our machine-learning classification results and led to more robust correlations between scale-free features and patients' symptom scores.

A drawback of the DFA study was that it did not include the striatum as one of the deep structures in its analyses. Recent findings have shown that dopamine in associative striatum pathways is perhaps more involved in the pathophysiology of schizophrenia and needs to be considered (McCutcheon et al., 2019). Future studies should thus include this brain structure in their source-reconstruction estimation for a more comprehensive understanding of this psychopathology.

A further limitation of our studies is that the recruitment of patients, like most - if not all - previous studies, was based on the DSM's classification system. In research, the use of DSM labels can lead to the artificial grouping of patients which might not reflect the actual symptomatic profile of patients. Nevertheless, the use of DSM categories has clear advantages and disadvantages. The application of DSM labels has allowed for significant scientific progress toward understanding the neural mechanism of psychopathologies, and towards the development of treatment targets. Moreover, while the DSM has standardized diagnoses and treatment in clinical practice, its' poor validity has hindered progress in clinical research. A substantial risk of misdiagnosis exists when using the DSM as it does not account for the heterogeneity and comorbidity of symptoms observed across and within patient populations (e.g. Hankin et al. 2005; Walton et al. 2011; Hengartner and Lehmann 2017). One contributing factor is that diagnostic titles can change as the symptoms of patients' evolve, particularly when mood and psychotic symptoms are intertwined. This might be in part due to the fact that many of the genes involved in the neurodevelopmental changes of SZ overlap with those of MDD and BD (Pain et al., 2018; Barkhuizen et al., 2020), with the true differences residing in the expression or mutation of those genes. Therefore, the DSM's symptom-based and timing-based approach not only affects treatment options for patients (low response rate

to medication), but also the research that guides clinical decisions (Kessler et al., 2003). As a consequence of the unclear boundaries between diagnostic entities, residual categories (not otherwise specified, NOS) are often used by clinicians to classify patients. One of the major concerns of the DSM systems of classification is that it relies primarily on the subjective opinion of the mental health practitioners; professionals depend on a mental template to which they match patients' clinical profiles (Maj, 2011). Finally, the diagnostic labels are problematic as they can be stigmatizing, with the affected individual internalizing those labels as their identity (e.g., using the term "schizophrenic" vs "individual who has schizophrenia"). The main reason DSM terminologies are still used in clinical practice is to allow mental health specialists to bill patients' treatment to their insurance companies easily. Indeed, the diagnostic label is needed for individuals to get reimbursed for their costly pharmaceutical and behavioural treatments. To some extent, although mental health professionals might prefer domain-based classification systems (see next section), they resort back to DSM diagnoses for insurance formalities, as proper treatment is prioritized above anything else.

In our studies, specifically, it is possible that using DSM-labels led to lower decoding accuracies in our machine-learning analyses, or to diminished correlational findings. Future work should lean on domain or dimensional-based classification systems for the diagnosis of mental health disorders, as it could help untangle the heterogenous findings in the neuroimaging literature and improve on group-level analyses and findings.

6.5 Future work

On way to circumvent the above-mentioned issues of the DSM classification system would be to employ a domain or dimensional approach to the categorization of disease. Thus, an interesting follow-up study would be to apply unsupervised machine-learning to a pool of psychopathologies with overlapping clinical symptoms (e.g., schizophrenia, schizoaffective, depression, bipolar disorders). The aim would be to see whether any emerging clusters of profile, based on dimensional features, would better characterize patients than the strict DSM diagnostic boxes, and help the movement of psychiatry towards precision medicine. This framework resembles the concept of two classification methods that have recently emerged to address the DSM's

limitations: the Research Domain Criteria (RDoC) (Insel et al., 2010; Insel, 2014) and the Hierarchical Taxonomy of Psychopathology (HiToP) (Kotov et al., 2017). The RDoC aims to integrate different levels of objective and subjective information (from genetics to self-report) to improve diagnoses. It uses five core domains (negative valence, positive valence, cognition, social processes, arousal and regulation) to quantify behaviour along a spectrum based on a deficit in a mechanism (e.g., cognition or arousal) instead of rigid categories, such as those found in the DSM. The HiToP is based on hierarchical dimensions that are empirically founded, and is said to address the DSM's limitations of heterogeneity, co-morbidity, diagnostic instability and variability, and arbitrary temporal boundaries (Kotov et al., 2017). This approach uses a spectrum (from internalizing symptoms, to thought disorder, detachment, etc.) to categorize symptoms. Moreover, this system relies on scientific data rather than expert opinion to make decisions. Consequently, it has been suggested that domain or dimensional classifications of individuals could provide stronger correlations between symptoms and neurobiological markers than DSM criteria. Unsupervised data-mining could thus help untangle the heterogenous findings in the literature in terms of connectivity analyses, by revealing distinct sub-groups of schizophrenia patients, and improving our understanding of the neural mechanisms involved in psychopathologies. Coincidently, a number of researchers have recommended this approach (Bzdok and Meyer-Linderberg, 2018), and a few have implemented it in schizophrenia (Kanchanatawan et al., 2018), depression (Yang et al., 2020), ASD (Urchs et al., 2020) and Alzheimer's disorder (Tam et al., 2019).

An extension to the last paper (Chapter 5), would be to test how differences in resting-state dynamics present themselves in autism spectrum disorder (ASD). Similar to schizophrenia, ASD patients show difficulties in adapting to- and assimilating information from their environment, and are particularly sensitive to eye-contact (Park et al 2016). Given the simplicity of EO and EC resting-state paradigms, this imaging approach could be an elegant way to reveal new neuromechanistic underpinnings in a cohort that is typically difficult to test in research settings. A third extension of our findings would be to include siblings or twins (i.e. to look at unaffected siblings vs. affected siblings) and examine whether similar markers of scale-free dynamics can be observed in those with the same genetic makeup, or if they are unique to individuals who have a full-blown onset of psychosis. The purpose of this work would be to investigate the effect of

genetic expression on scale-free dynamics. A forth extension of this thesis would be to measure the resting scale-free parameters of the MEG signal within a longitudinal study, following a large cohort of at-risk youths who have a genetic or behavioural predisposition for psychotic disorders. Longitudinal studies are an important step in the development and evaluation of the sensitivity and specificity of biomarkers. A fifth extension of this work could be the use of multifeature machine-learning approaches. Through the combination of non-linear measures of dysconnectivity, anatomical patterns of dysconnectivity and gene-candidates (e.g., COMT Val/Met polymorphism), we could measure whether the classification accuracy of patients and healthy controls could be improved, and help narrow-in on a practical set of biomarkers for schizophrenia.

6.6 Summary of MEG-depression study and challenges

A final projection for this thesis would be to transition the study of self-similarity and multifractality in other psychiatric diseases, such as depression. Such a study was in fact designed as part of this PhD thesis, and resting-state and task-based MEG data were meant to be acquired and analyzed in major depressive disorder (MDD) patients. While important progress was made in terms of the theoretical background, task design, ethics approvals, stimuli validation and piloting (see Appendix C), we were not able to acquire the MEG data within the timeframe of this PhD thesis.

Specifically, I designed and set-up an experiment to address the questions about a) how scale-free dynamics are altered in major depressive disorder (MDD) patients, and b) which scale-free metric best discriminate between MDD patients and healthy controls, using resting-state MEG, anatomical MRI and machine-learning algorithms. I also sought out to evaluate the potential beneficial effects of visualizing humorous videos on the resting-state MEG patterns of MDD patients, and to measure the effect of humorous video clips on subjective mood ratings (e.g., happiness, nervousness, alertness), objective physiological measures (e.g. heart rate), and memory (e.g., face recall). The rational, explicit hypotheses and protocol are included in the Appendix. Briefly, the rational for the second portion of the study is rooted in positive psychology. According to this field, interventions such as humour can help depressive patients break away from their deep-rooted cognitive biases, and is thought to improve depressive and anxiolytic symptoms, as well as

memory and immune system, across all type of populations (Bennett et al., 2003; Ko and Youn, 2011; Konradt et al., 2012). It has been suggested that this type of therapy helps patient by not only reducing negative emotions but, also, by building positivity and resilience towards future adverse events.

Important progress was made over the past few years towards achieving our goals for this study. For instance, we have completed a validation study based on a database of humorous videos that we created; this online study was completed by hundreds of volunteers, from varying cultural backgrounds. The study aimed to better understand what made people laugh and to see how age and gender affected preferences n humorous content. This step was important in order to compile the best possible stimuli set for the neuroimaging portion of the study. A preliminary EEG study provided quantified validation for the videos, and also showed that the extent of amusement during video viewing can be decoded from resting state brain activity using supervised machine-learning (Toupin et al., *in prep*). In parallel, the MEG paradigm was fully coded with Psychopy, and successfully implemented in a handful of test-pilots. However, our progress was met with important challenges, which prevented us from collecting the core MEG and MRI data from patients and controls in the scheduled timeframe. First, the multimodal and multisite nature of the study involved the acquisition of three levels of ethics to conduct the study (i.e. at the clinical site, the MRI centre and MEG centre). This resulted in unavoidable administrative delays in obtaining ethics (>10 months). Additionally, this project faced headwinds of technical issues with the MEG projector (down for >8 months), which prevented scanning availability and drastically restricted recruitment, all of which occurred before the COVID-19 pandemic put all research work on hold for the foreseeable future. For once data collection can resume, the full ethics, protocol and experimental paradigm (e.g., coding of the MEG task) has been tested and completed, and is ready to be implemented by a future graduate student.

6.7 Implications of the findings for research and society

The findings of our studies have extensive impact on future research studies. First, considerations should be taken when choosing between EO and EC resting-state MEG paradigms, based on networks of interest. Second, these studies encourage the study of arrhythmic brain activity in

psychopathologies. They underlined the importance of examining multifractality in addition to self-similarity, when interested in characterizing scale-free dynamics in the neural signal. Until recently, there has been a hyper focus on task-based changes in neural dynamics, particularly looking at the rhythmic oscillatory part of the signal. However, as many researchers have unveiled, the "1/f background noise" that makes up most of the brain signal is not actually "noise", as first presumed. This arrhythmic activity is thought to carry key information on brain organization, information processing, storage and communication, all of which are often altered in psychopathologies. Thus, we propose that perturbation in the arrhythmic neural signal actually underlines the cognitive symptoms observed in mental disorders. The results of this study could potentially open-up to, both, a new pathway of biomarkers for the early detection of those at-risk of developing schizophrenia, and for new therapeutical targets.

From a societal perspective, the findings of this PhD highlight the potential utility of using MEG for diagnostic and prognostic purposes. One way to improve on early detection of psychosis is to improve on reliable and easily accessible biomarkers. In the future, it is possible that EEG and MEG would be seamlessly integrated in hospital settings for the potential purpose of identifying at-risk individuals who might develop mental health or cognitive challenges. One of the barriers of routine clinical use of MEG, is cost. Thus, before expensive imaging techniques are implemented, the emphasis should be on identifying accurate biomarkers, which could justify the costs.

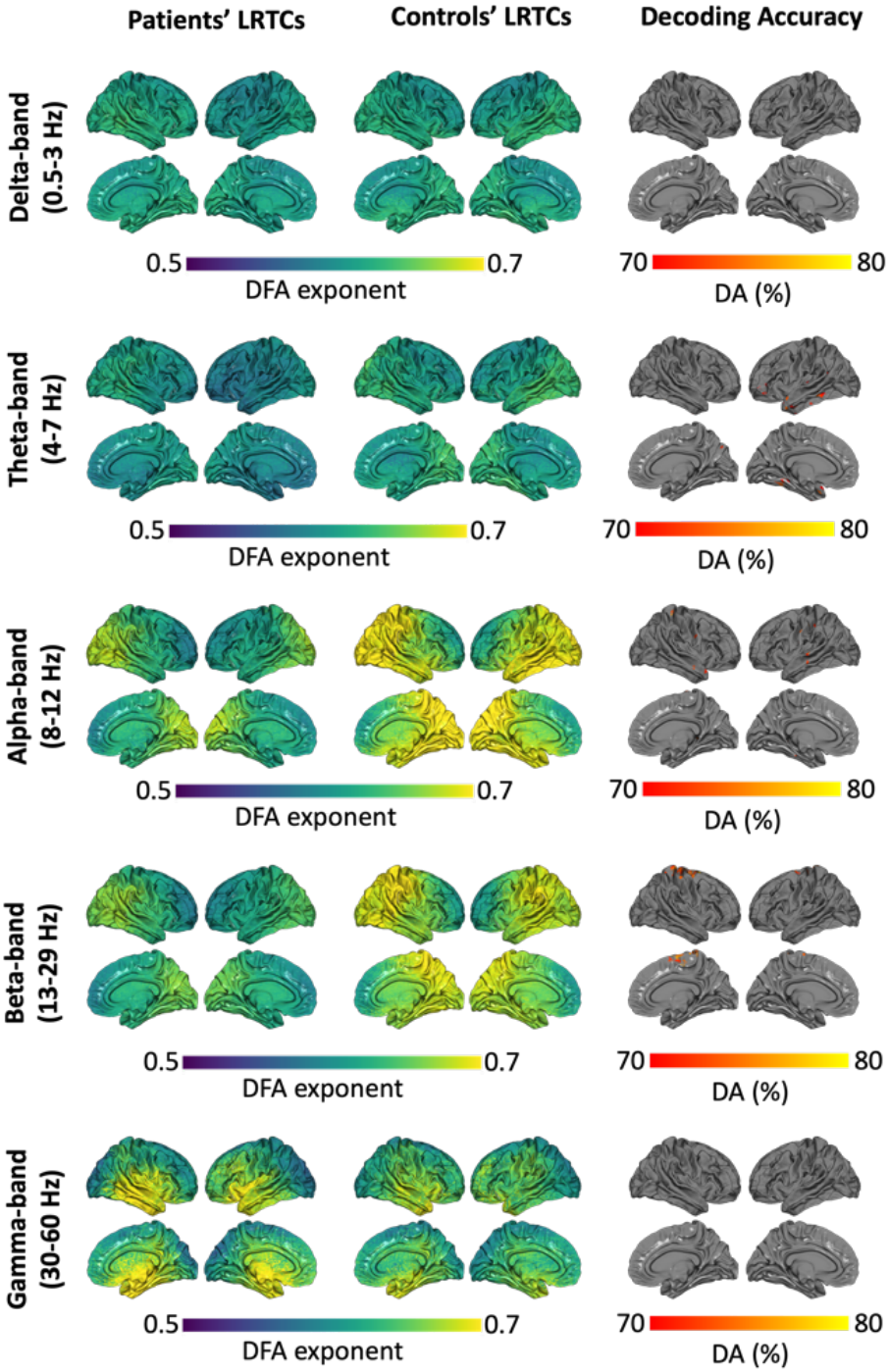
Age is also an important factor to take into account. Schizophrenia typically arises during a critical period, during the transition of childhood to adolescence (van den Heuvel and Kahn, 2011). During typical neurodevelopment, neural connectivity patterns change as the brain matures, and LRTCs have been found to increase during this transitional period (Smit et al., 2011). It would be impactful to have predictors in young children/adolescence who are at risk of developing psychopathologies. Early diagnosis would allow, for better management of symptoms, and for the empowerment of patients. Indeed, giving back autonomy to individuals who have schizophrenia is vital to their well-being and future success in society. The routine emergency care that is currently in place for patients experiencing psychotic episodes are typically forced-onto them and, while this approach might be needed at times, better management of care centers are needed. Improving on early

diagnoses and providing patients with tools to manage their symptoms can also prevent long-term trauma from these types of experiences. For instance, if early diagnosis is feasible, more efforts could be made to prevent those at-risk from experimenting with drugs and alcohol, especially at a young age. Research has shown that that early cannabis users, with behavioural dispositions, are at a higher risk of developing psychosis than other adolescence (Henquet et al., 2005). Cannabis, which is linked to the dopaminergic reward system, increases dopamine in cortex and mesolimbic pathway, and might be the psychosis-trigger in pre-disposed adolescents. Thus, it is important to equip those at genetic and behaviour risk in the best way we can in order to give them a chance at a healthy and fulfilling life.

Chapter 7: Conclusion

In the psychiatry literature, there is substantial knowledge of the abnormal behavioural, cognitive and neural properties of patients. The present PhD work sheds light onto a perspective that is often ignored in the study of the neural mechanisms of psychopathologies: the relationship between resting-state scale-free dynamics and altered information integration and communication. The baseline activation and spatiotemporal organization of the brain is complementary to task-based neural alterations, and both should be conduct in parallel in clinical research. Finally, this doctoral thesis lays the groundwork for future studies by strongly contributing to an emerging new body of evidence that has shifted the discussion of dysconnectivity in schizophrenia towards the temporal dimension, and by highlighting important methodological considerations for prospective research endeavours.

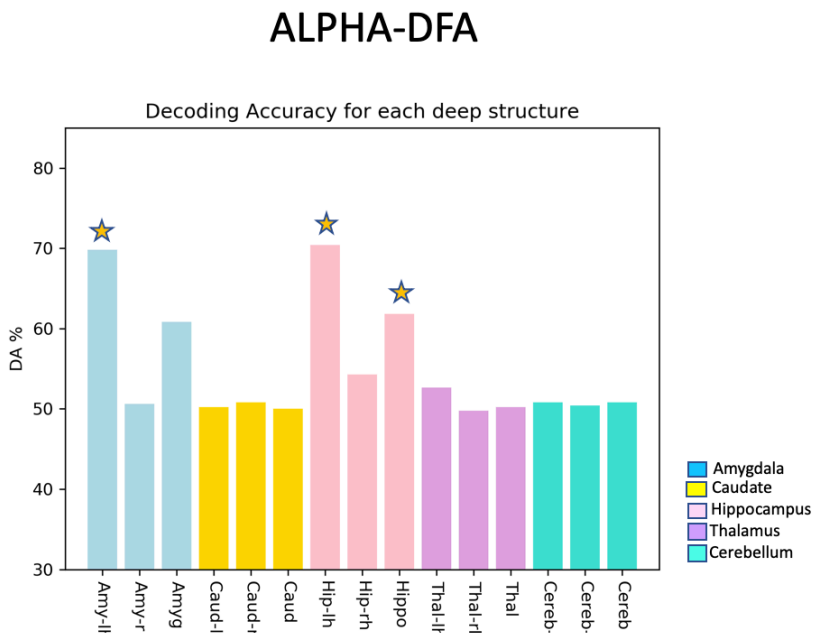
Appendix A: Supplementary material for Chapter 2



SUPPLEMENTARY FIGURE 1 : LONG-RANGE TEMPORAL CORRELATIONS IN SCHIZOPHRENIA PATIENTS AND CONTROLS.

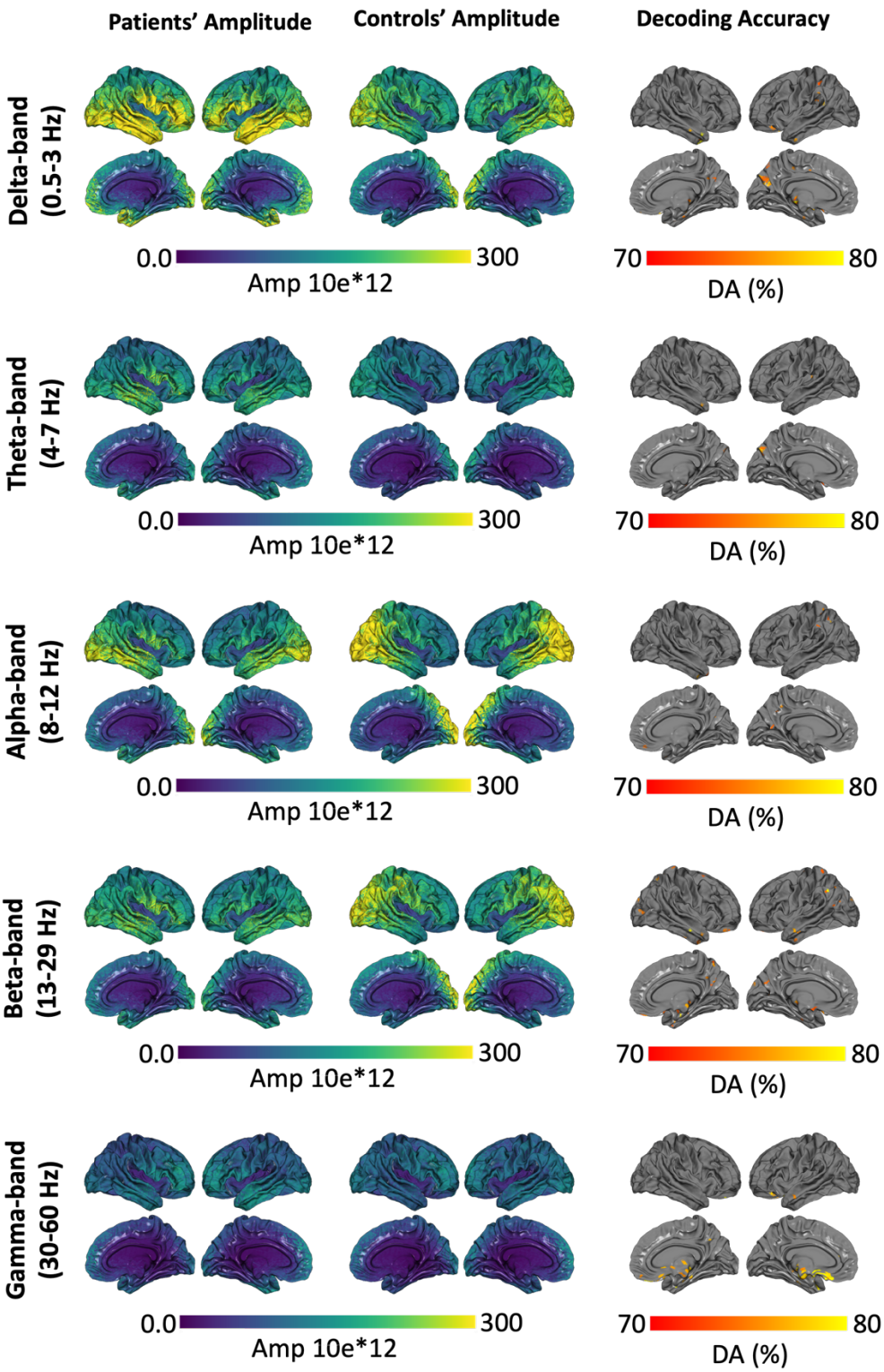
Columns 1 and 2 show mean LRTC values for each group. Column 3 shows the decoding accuracy of DFA exponent/LRTCs using SVM, 10-fold cross validation, with applied max statistics and 1000 permutations. Only statistically significant decoded regions are shown ($p<0.005$). DA = decoding

accuracy, DFA = detrended fluctuation analysis, LRTCs = long-range temporal correlations, SVM= support vector machine



SUPPLEMENTARY FIGURE 2: CLASSIFICATION OF SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS BASED ON LRTCS AT THE SUBCORTICAL LEVEL

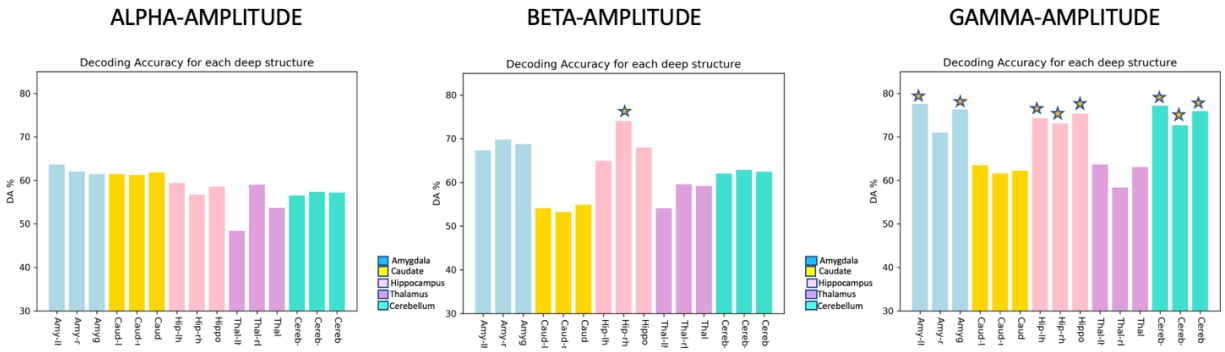
SVM classification of groups, using alpha DFA exponents (LRTC) as discriminant features computed in deep structure ROIs. Statistically significant decoded ROIs are indicated with a star ($p<0.001$). The suffix "-lh" indicates left hemisphere, "-rh" indicates right hemisphere, and no suffix reflects classification using both left and right hemispheres. Amy = amygdala, Caud = caudate, Cereb = cerebellum, DA = decoding accuracy, DFA = detrended fluctuation analysis, Hipp = hippocampus, LRTCs = long-range temporal correlations, SVM= support vector machine, Thal = thalamus



SUPPLEMENTARY FIGURE 3: SOURCE-LEVEL RESULTS OF SPECTRAL AMPLITUDE OF SCHIZOPHRENIA PATIENTS AND THE CONTROL GROUP

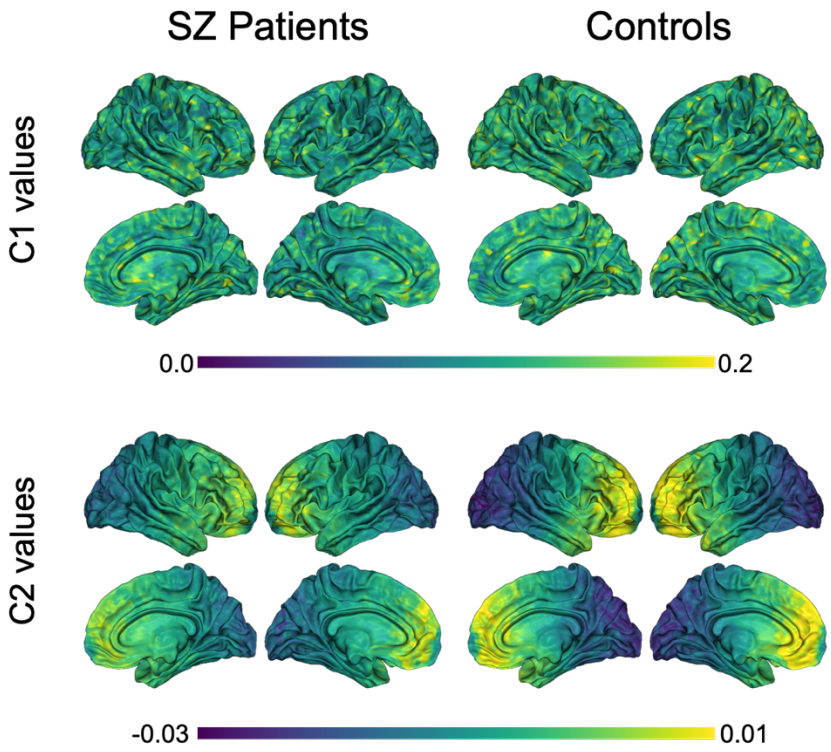
Columns 1 and 2 show averaged amplitude values (A-m * 10^12) for each group at each node. Column 3 shows the decoding accuracy of spectral amplitude using SVM, 10-fold cross validation, with applied

max statistics and 1000 permutations. Statistically significant decoded regions are shown (p<0.005). Amp = spectral amplitude, DA = decoding accuracy, SVM= support vector machine

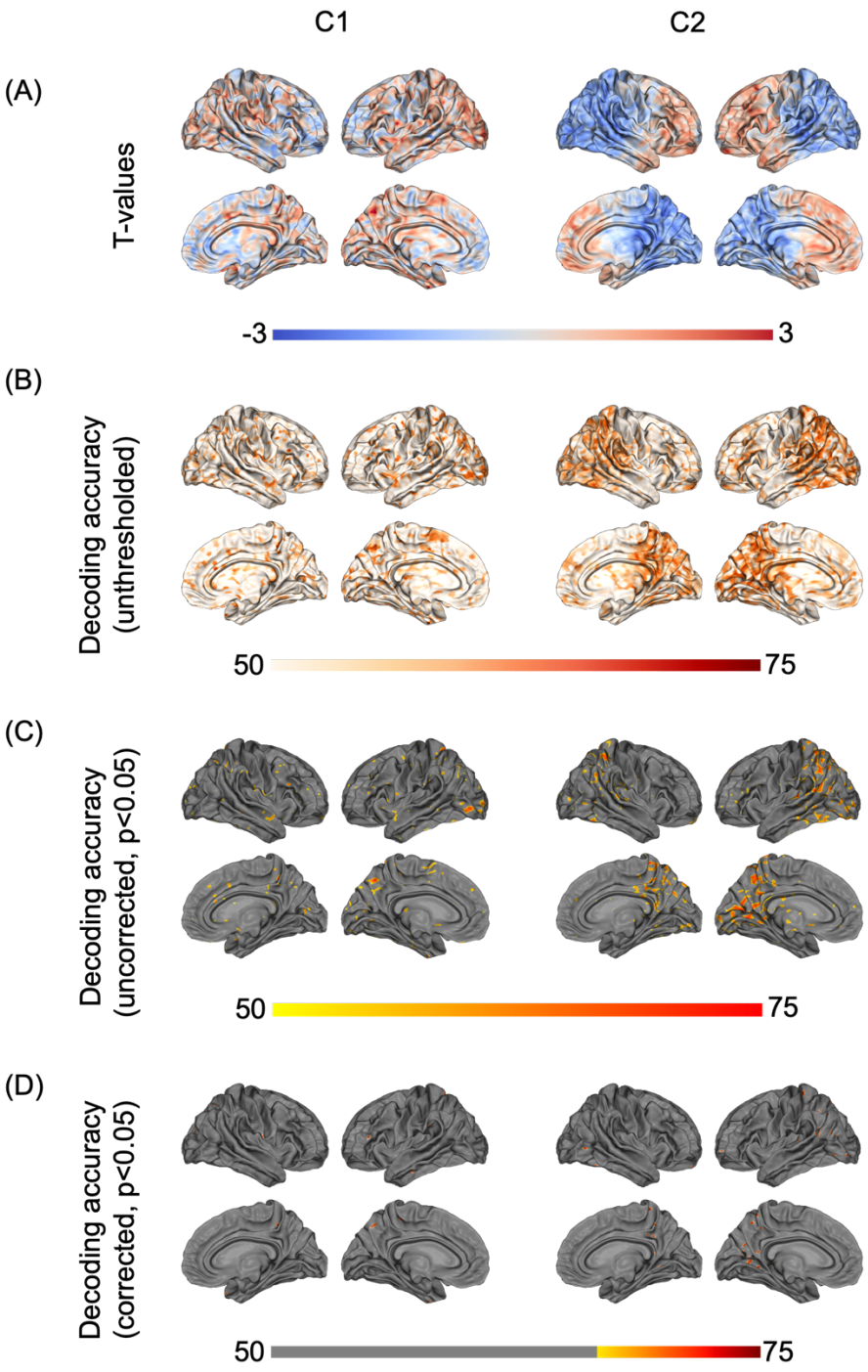


SUPPLEMENTARY FIGURE 4: CLASSIFICATION OF SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS BASED ON SPECTRAL AMPLITUDE AT THE SUBCORTICAL-LEVEL
SVM classification of groups, using 10-fold cross validation, with applied max statistics and 1000 permutations. Statistically significant decoded ROIs are indicated with a star (p<0.001). The suffix "-lh" indicates left hemisphere, "-rh" indicates right hemisphere, and no suffix reflects classification using both left and right hemispheres. Amy = amygdala, Caud = caudate, Cereb = cerebellum, DA = decoding accuracy, Hipp = hippocampus, LRTCs = long-range temporal correlations, ROI = region of interest, SVM= support vector machine, Thal = thalamus

Appendix B: Supplementary Material for Chapter 4



SUPPLEMENTARY FIGURE 5: GROUP AVERAGES OF C1 AND C2 VALUES IN SZ PATIENTS AND CONTROLS USING P=4
Averaged C1 and C2 values were computed for each of the 8196 nodes, within each group, using p=4. SZ= schizophrenia



SUPPLEMENTARY FIGURE 6: GROUP DIFFERENCES AND MACHINE-LEARNING RESULTS USING P=4

(A) shows t-values from the unpaired t-tests (non-significant), showing (controls – patients). (B) shows unthresholded DA values based on logistic regression, using C1/C2 as a single feature. (C) shows the same DA values, thresholded at $p<0.05$. Finally, (D) shows the DA values corrected for multiple comparisons using maximum statistics ($p<0.05$), thresholded at the chance level of 70%. P-leader p=4 was used here. DA= decoding accuracy.

Appendix C: Groundwork for an MEG resting-state study in Major Depressive Disorder

A part of my PhD time was invested in the design and implementation of an MDD MEG experiment. Despite great progress in the design, ethics approvals, validation of stimuli, coding of MEG scripts and pilot testing, I was not able to acquire the MEG data within my doctoral studies, due to extenuating circumstances outside of my control (e.g., technical difficulties with the MEG, global pandemic). Nevertheless, for the sake of completeness and documentation of the work that has gone into this study, I provide below the details as an appendix.

B.1 Rationale

Depression is the most common and most studied psychiatric illness in humans. Major Depressive Disorder (MDD) is characterized by features such as low mood and/or a loss of interest in daily activities for an extended amount of time and, typically, involves ruminative, self-referential thoughts (American Psychiatric Association, 2013b).

B.1.1 Alterations in local and global networks in MDD across neuroimaging modalities

We recently published an exhaustive review of local and long-range synchrony findings in MDD and bipolar disorder across fMRI, EEG and MEG (Alamian et al., 2017a). Briefly, in terms of EEG-based local synchronizations, enhanced power in slow (<20Hz) oscillations have been observed among MDD patients across the brain (Koo et al., 2015; Northoff, 2016; Olbrich et al., 2014). A MEG study has however found different results, with decreased power in theta and alpha frequency bands, but enhanced power in beta band (Jiang et al., 2016). In terms of long-range synchronizations, across neuroimaging modalities, it is observed that MDD individuals have enhanced connectivity pattern within nodes of the DMN (Whitfield-Gabrieli and Ford 2012; Northoff 2016), altered connectivity between areas of the DMN and the limbic system (particularly between the subgenual anterior cingulate cortex, ACC, and hippocampus, Greicius et al. 2007; Nugent et al. 2015), hypoactivity between dlPFC and amygdala (Dannlowski et al. 2009; He et al.

2016; Pathak et al. 2016), hyperconnectivity between the subgenual ACC and dlPFC (Olbrich et al. 2014; Pathak et al. 2016), and hyperconnectivity between the insula and the amygdala (Avery et al. 2014; Nugent et al. 2016). Overall, connections projections from and to the subgenual ACC and the dlPFC, appear to be critical in the treatment and expression of depressive symptoms.

B.1.2 Alterations in scale-free dynamics in MDD

Within rhythmic brain activity, broadband EEG-based LRTCs were found to be normal, albeit higher than average, in MDD patients over frontal, central, temporal and occipital sensors, compared to controls, with their clinical symptoms correlating positively with the scaling exponent (Lee et al., 2007). More recently, an EEG study found the opposite patterns, where LRTCs were attenuated in patients compared to controls in the DMN (Wang et al., 2016a). These contradictory findings can be attributed, like in SZ, to age, medication and illness duration.

Within arrhythmic brain activity, Wei and colleagues led two fMRI studies (Wei et al., 2013, 2015), where they measured broadband scale-invariance using the measure of General Hurst Exponent, GHE. Increased GHE values were observed in the ventromedial prefrontal cortex and in the salience network, while decreased values were observed within the DMN. Akar and colleagues' review of EEG complexity findings in MDD (Akdemir Akar et al., 2015) partly supports these findings. They found fractal dimension and entropy metrics to be typically increased among patients compared to controls during both resting-state and emotional induction, particularly over clinically relevant brain areas, such as the frontal and parietal brain regions. In RS-MEG, antidepressants appeared to normalize complexity in patients, which was observed to be higher than controls prior to pharmacological treatment (Mendez et al., 2012).

Taken together, it is obvious that more work is needed in the study of scale-free properties in MDD, along with comparison between these metrics and classical connectivity methods using MEG data in sensor and source space (Lee et al., 2007).

B.1.3 Investigation of Humour on the brain and on mood

B.1.3.1 Negative bias theory in depression

One of the leading theories for mood disorders is that depressive and anxious symptoms might emerge due to a negative interpretation of external events (Abramson et al., 1989). Over time, this would reinforce a biased integration of information arising from their surroundings, or from within themselves. Thus, during a stressful moment, a person might have the tendency to wrongfully attribute the cause of an incident to global and stable reasons that highlight their own personal inadequacies. This cycle would result in self-derogatory affect that could lead to maladaptive beliefs about themselves (e.g., worthlessness, hopelessness; Malhi et al. 2015). While MDD patients typically experience anhedonia during their episodes (Malhi et al., 2015), and pay less attention to positive stimuli (Bianchi and Laurent, 2015) it is known that neural response to emotional stimuli can be altered by pharmacological interventions, such as escitalopram (Malhi et al., 2015), as well as psychotherapy. Interestingly, it is thought that this shift in emotional processing occurs through the move towards a similar positive bias (Outhred et al., 2014), as the ones healthy individuals generally exhibit.

B.1.3.2 Benefits of humour and how it can alter brain patterns

According to recent studies, positive psychology, and specifically humour, can also help depressed individuals break free from their cognitive bias cycle. Indeed, significant and lasting improvements in depressive symptoms, anxiety, memory, and immune system in both clinical and healthy populations take place after such interventions (e.g., Bennett, 2003; Kim et al., 2015; Konrad et al., 2012; Ko & Youn, 2011). Frietas and colleagues (2016) argued that positive therapy might treat depression by not only reducing negative affect, but also by building positive emotions, resilience towards adverse events and future depressive episodes, and by giving meaning to patients' lives. The beneficial effects of humour can be observed across the brain's fronto-limbic pathway, and are thought to occur even if an individual's personal ratings of funniness is wavering (Vrticka et al., 2013). This is particularly relevant among depressed populations who might not overtly laugh at humorous stimuli.

B.1.3.3 Current limitations in the field of humour studies

While a few fMRI studies have explored how humour is processed in healthy and pathological populations, to date no study has explored the effect of humour on the neural circuitry or complexity of MDD patients using MEG. One EEG study that explored the induction of positive

emotion through musical stimulation found healthy subjects' brain signal complexity, as measured by different metrics (e.g., fractal dimension, entropy, Lempel-Ziv complexity), to decrease after listening to music compared to listening to noise (Akdemir Akar et al., 2015). We could thus predict that a similar effect could be brought on by humorous videos. Given the substantial body of work on negative emotions, empirical evidence for the benefits of positive emotions on the neural organization of patients should be investigated.

B.2 Objective

The goals of his study are three-fold: (1) to understand how scale-free properties are altered in MDD patients using RS-MEG and, identify which among them can best discriminate between MDD patients and controls using machine-learning algorithms; (2) determine the potential correlations between all these measures with MDD patients' clinical symptoms scores on depression, anxiety and stress scales; (3) understand the potential beneficial effect of humorous video clips on RS-MEG patterns of MDD patients and, characterize the effect of humorous video clips on subjective mood ratings (e.g., happiness, nervousness, alertness) and objective physiological measures (e.g. heart rate) among MDD patients.

Based on the cognitive bias theory, I hypothesize that the properties of rhythmic and arrhythmic brain activity will be altered in MDD patients compared to controls. Thus, I predict atypical scale-free dynamics in MDD patients compared to controls, which significantly correlate with patient's clinical scores. Based on the literature on positive psychology, and given that RS organization appears to correlate with MDD patients' cognitive and emotional symptoms (Drevets et al., 2008; Mulders et al., 2015), I hypothesize that viewing humorous videos will somewhat normalize the intrinsic neural networks of MDD patients and improve their subjective mood. Thus, I predict that viewing humorous videos will, at least, temporarily normalize RS-MEG patterns among MDD patients, such that they resemble those of healthy individuals, as measured by classical connectivity measures and graph theoretical model. In addition, I predict participants to show an increase in levels of happiness, alertness, and relaxation, as well as better memory performance, after viewing humorous videos compared to baseline.

B.3 Method

Ethics certificates for all parts have been granted from the Comité d'éthique de la recherche en arts et en sciences (CERAS-2017-18-100-D), the CIUSSS du Centre-Sud-de-l'Île-de-Montréal and the CÉR-CEMTL.

B.3.1 Participants

For the beta-testing of the videos, >150 subjects will be recruited online. Subjects will consist of male and female subjects from North America and Europe recruited through word of mouth, and online advertisement on social media outlets (e.g., Facebook, Twitter and Linked-In). The MEG study will recruit 60 participants and take place in Montreal, at the Université de Montréal (UdeM). This sample size is based on the power-analysis for a moderate-strong effect size in group differences (0.70), a significance level of a = 0.05, and statistical power of 80%. Thirty individuals recently diagnosed with MDD by a licenced psychiatrist will be included and 30 healthy controls matched for age and gender. Patients will be recruited through our clinical collaborator at the *Centre de recherche de l'Institut universitaire en santé mentale de Montréal*. Healthy controls will be recruited through advertisements posted online and throughout universities in the Montreal area.

Across both parts, subjects will consist of adults, between the ages of 18 and 50 years old. Participants with bad or uncorrected vision, and/or inability to commit to the full-length of the testing period will be excluded. For part ii, healthy individuals will be excluded for any of the following: past or present neurological or psychological illness, history or active substance dependence/abuse, memory impairments, or first degree relatives with mental disorders. For the MDD group, individuals will be excluded for any of the following reasons: inability to complete the first half of the MEG study, more than two major depressive episodes, severe score on the Beck's Depression Inventory. Finally, for part ii, individuals will be excluded if they present with any contraindications that does not allow them to complete the MEG and/or MRI scan.

B.3.2 Experimental paradigm

B.3.2.1 Behavioural , video testing, stimuli evaluation (*completed*)

Beta-testing of the videos will be conducted online through the website humouresearch.com created with Dr. Anne-Lise Saive, post-doctoral student, and volunteers in the CoCo Lab. The experiment will be available in French, English and Spanish, and will last around 15 minutes. Before starting the experiment, participants will be asked to give their electronic consent after reading the details of the experiment. Each subject will then view and rate a series of video clips of humorous and neutral (but interesting) content, each lasting between 8-12 seconds. Given that this part of the study will help guide parts of the MEG study, special attention will be given to the selection of the stimuli to ensure that they are matched in length and resolution. Moreover, given that verbal fluency is known to be diminished among MDD patients (Fossati et al. 2003; Uekermann et al. 2008), the chosen humorous stimuli will consist of non-verbal, video clips, depicting "slap-stick" jokes, easy to understand by any individual from any background or ethnicity.

B.3.2.2 MEG experiment

Subjects that show interest in the study will have read the consent form and safety information for both the MRI and MEG scans prior to their arrival to the UdeM. Participants will be called one week prior to the start of this experiment to ensure that they are compatible with both imaging machines.

The day will start with participants giving their written consent, and completing a written screening form to ensure their safe entry into the MEG scanner, a 275 channels CTF machine located in the Marie-Victorin pavilion, in the department of Psychology at the UdeM. They will then be asked to answer demographic questions (age, gender, education level, ethnicity, and handedness), and complete questionnaires about their humor style (Martin et al. 2003). Moreover, all participants will complete the following scales: Beck's Depression Inventory-II (BDI-II), Beck's Anxiety Inventory (BAI), Cognitive Distortion Scale (CDS), Perceived Stress Scale (PSS), the Sense of Humor Questionnaire (Svebak, 1996, 2010), and a brief questionnaire (Likert 7-point scale) on current levels of happiness, nervousness, alertness. In addition, MDD patients will be asked to

provide information regarding medication and treatment history and current pharmacological dosage, age of illness onset and number of previous depressive episodes.

During the preparation phase of the experiment, reference electrodes will be placed on the participant to capture muscle, cardiac and ocular artefacts. Participants' heart rate and electrodermal responses will also be monitored in order to evaluate the different physiological effects of viewing the videos. The MEG paradigm is made of two parts. The first part consists of three resting-state blocks lasting five-minutes each, which are interspersed with two five minute-long videos (humour and neutral). The videos will be chosen based on the databsase created in the first part of this study, and humourous and neutral video blocks will be counterbalanced. During the videos, participants will be asked to simply watch and pay attention to the videos. The second part of the experiment consists of three blocks of two-minute-long emotion-recognition tasks, interspersed with two blocks of humourous and neutral videos. During the task, participants will be asked to identify the facial emotion presented (happy, sad, angry, surprise, neutral). The stimuli are sourced from a database called *FACES* from the Max Planck Institute for Human development in Germany. Full description and validation of this database has been previously published (Ebner et al., 2010). The last emotion recognition block will be followed by a short memory test, where participant will be asked whether they recognize the presented faces (yes, no). This test will primarily allow us to assess alertness levels and quality of the memories they formed. The 40-min experiment will end with brief questions about their current mood levels

Either on the same day, or within a week of the MEG experiment, a T1-anatomical scan will be acquired for each participant using the 3T Siemens MRI machine, located at the *Unité de neuroimagerie fonctionnelle*, located in the *Centre de recherche de l'institut universitaire de gériatrie de Montréal*.

B.3.3 Analyses

To identify the atypical neural network patterns of MDD patients, the first (baseline) RS-MEG data of each group will be extracted. Next, to evaluate the effect of humour on RS networks and mood, the first (baseline) and third (after viewing humorous video) RS-MEG data of subjects will

be used. Once again, all analyses will be conducted both at the sensor and the source level. Source and scale-free analyses will be the same as for the SZ study.

B.3.3.1 Connectivity analyses

Functional connectivity will be computed throughout the brain of each subject group. Local synchrony will be quantified through spectral power estimation and time-frequency analysis. Long-range, inter-areal, connectivity of the RS-MEG signal will be explored using a number of neuronal coupling measures, such as imaginary coherence (Nolte et al. 2004) and weighted phase-lag index (wPLI, Vinck et al. 2011). In addition to classical connectivity measures, graph theoretical metrics will be assessed. Among others, small-worldness, modularity and rich clubs will be computed for both cohorts. Graphs will be built following standard methods such as the ones reviewed by Bullmore and Sporns (2009).

B.3.3.2 Statistical Analyses

Similar to Chapter 3, group analyses will be conducted between MDD patients and their controls to see how they differ in terms of connectivity metrics, graph theoretical features and scale-free dynamics, using their RS-MEG data. Two-tailed, un-paired, non- parametric tests will be used, corrected with maximum statistics using exhaustive permutations (number of permutations = 1000) (Pantazis et al. 2005). A number of correlational analyses will also be conducted between connectivity and graph theory metrics and scale free dynamic measures, as well as age, age of onset, number of depressive episodes, gender, BDI/BAI/PSS scores, and medication information.

Using the MEG data, within group statistical analyses will be conducted to see if and how humorous video-clips changed RS-MEG patterns in MDD patients, and controls in terms of connectivity metrics and graph theoretical features. To address these questions, repeated measures analysis of variance will be applied, using age, gender, ethnicity, education level, and humour style scores as covariates. Correlational analyses will also be conducted between all the metrics and demographic variables. Finally, we will look at the correlations between videos (humorous and neutral) and mood levels (happiness, nervousness) measured before and after viewing the videos. Correlation between the videos and the physiological measures (heart-rate, electrodermal response) will also be explored.

B.3.3.3 Machine-learning

Similar to the SZ studies, I will first apply machine learning to subjects' scale-free values, as well as connectivity findings, to evaluate the discriminative power of the various electrophysiological features in objectively classifying patients and controls. Then, for the humor portion, the feature space will also include behavioral/physiological measures (as well as ratings of the videos and the evaluation of mood) in addition to the connectivity and scale-free metrics. The behavioral and/or neuronal features that provide the best prediction accuracy will unravel the most prominent correlates/markers of humor on physical and cognitive aspects of participants.

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