



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



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- Systematic review of Resting-state Magnetoencephalography (RS-MEG) studies in schizophrenia.
- We compare RS-MEG findings to those from RS-fMRI, RS-EEG and task-based MEG studies.
- Current challenges are described, methodological recommendations for future studies are proposed.

ABSTRACT

Objective: 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.

Method: 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.

Results: 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.

Conclusion: 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.

Significance: MEG-based resting-state power and connectivity findings could be great assets to clinical and translational research in psychiatry, and SZ in particular.

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Abbreviations: ACC, anterior cingulate cortex; CEN, central executive network; DBS, deep brain stimulation; DMN, default mode network; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PFC, prefrontal cortex; RS, resting-state; SZ, schizophrenia.

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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., 2017). 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, has 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, 2017; 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 (Luo et al., 2010). 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 and 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 4 provides a systematic account of resting-state MEG findings in schizophrenia population published to date, including alterations in local oscillatory power (Section 4.1) and changes in long-range inter-areal coupling (Section 4.2). The strengths and limitations of the reviewed resting-state MEG studies are then discussed in Section 4.3, which is followed by a discussion on the link between task-based and task-free findings in SZ with MEG (Section 4.4). Section 5 presents a critical account of methodological considerations, pitfalls and recommendations for future research. Finally, Sections 6 and 7 provide a general discussion and concluding remarks.

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 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., 2015; Giraldo-Chica and Woodward, 2017). 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, 2017). 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, disrupted effective connectivity in particular, 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 salience 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., 2015; Sheffield and Barch, 2016).

Finally, several studies indicate that the salience 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 salience network components (dorsal ACC, anterior insula) and CEN (dorsolateral PFC), and between salience 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).

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 over-viewed 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).

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.

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 (13–20 Hz), 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.

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.

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-modeling 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

Table 1

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.

Paper	Frequency range (Hz)	Methods	Patients	Controls	Main findings
Cañive et al. (1996)	n/a	<ul style="list-style-type: none"> Sensor-space average power 5 min eyes-closed 	<ul style="list-style-type: none"> 19 SZ (11 unmedicated) 	<ul style="list-style-type: none"> 10 controls 	<ul style="list-style-type: none"> ↓ 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	<ul style="list-style-type: none"> Sensor-space Dipole modeling 	<ul style="list-style-type: none"> 5 SZ 	<ul style="list-style-type: none"> 10 controls Age-matched 	<ul style="list-style-type: none"> ↓ δ, θ, α power and peak frequency in SZ compared to controls 8 weeks of aripiprazole treatment ↑ δ and θ levels, but α remained unchanged Dipoles were localized primarily to temporal and parietal brain areas
Sperling et al. (1999)	2–6 α : 7.5–12 β : 12.5–30	<ul style="list-style-type: none"> Dipole density PCA 	<ul style="list-style-type: none"> SZ 	<ul style="list-style-type: none"> Controls 	<ul style="list-style-type: none"> 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 β 1: 13–20 β 2: 21–29 γ 1: 30–45 γ 2: 46–60 γ 3: 61–71	<ul style="list-style-type: none"> Power differences at sensor level 5 min eyes-open 	<ul style="list-style-type: none"> 15 SZ 11 males Mean age: 30.2 ± 6.5 	<ul style="list-style-type: none"> 15 controls 11 males Mean age: 35.8 ± 9.4 	<ul style="list-style-type: none"> ↓ 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	<ul style="list-style-type: none"> Sensor-space estimation using SAM 10 s prior to button press and 10 s after a button press. At least 8 episodes of AH recorded each session 	<ul style="list-style-type: none"> 1 SZ Male Age: 8 yrs old 	<ul style="list-style-type: none"> n/a 	<ul style="list-style-type: none"> 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
Fehr et al. (2001)	δ : 1.5–4 θ : 4–8	<ul style="list-style-type: none"> Source-space power estimated with Dipole density, MNE 5 min eyes-open 	<ul style="list-style-type: none"> 28 SZ 22 males Mean age: 30.9 ± 9.6 40 SZ 23 male Mean age: 36.5 ± 3.9 	<ul style="list-style-type: none"> 20 controls 15 males Mean age: 34.4 ± 11.3 30 controls 15 males Mean age: 37.7 ± 4.0 	<ul style="list-style-type: none"> ↑ 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 ↑ 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
Sperling et al. (2002)	Slow: 2–6 Fast: 12.5–30	<ul style="list-style-type: none"> Dipole density plot ECD 10 min eyes-closed 	<ul style="list-style-type: none"> 30 SZ 18 males Mean age: 31.6 ± 8.9 	<ul style="list-style-type: none"> 17 controls 15 males Mean age: 32.4 ± 11.2 	<ul style="list-style-type: none"> ↑ density of dipoles generating δ and θ in SZ compared to healthy controls over temporal and parietal areas
Fehr et al. (2003)	δ : 1.5–4 θ : 4–8	<ul style="list-style-type: none"> Single ECD model Dipole density 5 min eyes-open 	<ul style="list-style-type: none"> 20 SZ 10 males Mean age: 37.5 ± 3.4 	<ul style="list-style-type: none"> 20 controls Mean age: 34.6 ± 3.4 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Single ECD model Dipole density 5 min eyes-open 	<ul style="list-style-type: none"> 29 SZ 17 males Mean age: 31.6 ± 8.9 	<ul style="list-style-type: none"> 18 controls 16 males Mean age: 33.1 ± 13.1 	<ul style="list-style-type: none"> ↑ 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	<ul style="list-style-type: none"> Dipole distribution plot, PCA 10 min 	<ul style="list-style-type: none"> 1 SZ Male age: 33 yrs 	<ul style="list-style-type: none"> 13 controls All male Mean age: 31.3 ± 4.7 	<ul style="list-style-type: none"> ↑ 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	<ul style="list-style-type: none"> Spatial distribution of dipoles estimated using 3-D convolution with a Gaussian envelope Dipole density plot 	<ul style="list-style-type: none"> 16 SZ 9 male 8 with AH Mean age: 33 ± 2.8 year 	<ul style="list-style-type: none"> 8 controls 4 males Mean age: 35 ± 8.2 	<ul style="list-style-type: none"> ↑ 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

Table 1 (continued)

Paper	Frequency range (Hz)	Methods	Patients	Controls	Main findings
Rockstroh et al. (2007)	δ : 1.5–4	<ul style="list-style-type: none"> Single ECD model ASWA/dipole density 5 min eyes-open 	<ul style="list-style-type: none"> 76 SZ or SA 62 males Mean age: 29.12 \pm 8.0 	<ul style="list-style-type: none"> 116 controls 59 males Mean age: 28.95 \pm 10.16 	<ul style="list-style-type: none"> \uparrow 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	<ul style="list-style-type: none"> Source-space power estimated with SAM Eyes-closed 	<ul style="list-style-type: none"> 38 SZ 27 males Mean age: 31.2 \pm 9.8 	<ul style="list-style-type: none"> 38 controls 27 males Mean age: 32.5 \pm 10.8 38 U.S. 11 males Mean age: 37.2 \pm 11.3 	<ul style="list-style-type: none"> \downarrow 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	<ul style="list-style-type: none"> Source-space power estimated with SAM 4 min eyes-closed 	<ul style="list-style-type: none"> 20 SZ 14 males Mean age: 31.2 \pm 10.9 	<ul style="list-style-type: none"> 20 controls 14 males Mean age: 31.3 \pm 10.8 	<ul style="list-style-type: none"> \downarrow 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	<ul style="list-style-type: none"> Source-space power estimated with sLORETA 2.5 min eyes-open 	<ul style="list-style-type: none"> 20 SZ 16 males Mean age: 22.8 \pm 3.9 	<ul style="list-style-type: none"> 20 controls 14 males Mean age: 22.1 \pm 2.0 	<ul style="list-style-type: none"> \uparrow θ, α, β power in SZ compared to controls in posterior cingulate cortex
Chen et al. (2016)	δ : 1–4 θ : 4–7	<ul style="list-style-type: none"> Source-space amplitude estimated with VESTAL 5 min eyes-closed 	<ul style="list-style-type: none"> 41 SZ 34 males Mean age: 37.63 \pm 12.09 	<ul style="list-style-type: none"> 37 controls 27 males Mean age: 38.92 \pm 11.13 	<ul style="list-style-type: none"> \uparrow 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

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 frequencies were found to be diminished in patients at baseline (Cañive et al., 1998). After 8 weeks of aripiprazole 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 (12.5–30 Hz) 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

Table 2

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.

Paper	Frequency range (Hz)	Methods	Patients	Controls	Main findings
Hinkley et al. (2011)	α : 8–12	<ul style="list-style-type: none"> Imaginary coherence Source-space estimation using Nutmeg software 4 min eyes-closed 	<ul style="list-style-type: none"> 30 SZ 23 males Mean age: 38.4 ± 11.1 	<ul style="list-style-type: none"> 15 controls 11 males Mean age: 43 ± 12.2 	<ul style="list-style-type: none"> \uparrow connectivity compared to controls in medial occipital gyrus in the left hemisphere, and in the right IFG \downarrow connectivity within the left dorsolateral PFC and the precentral gyrus Alterations correlated with psychosis, depressed mood, and impaired cognition No significant differences found between SZ and controls using coherence or graph theory metrics SZ showed trend towards \uparrow mean connectivity between frontal gyrus and the rest of the brain in θ and α bands, and \downarrow between PPC and the rest of the brain in γ-band \uparrow coherence levels compared to controls in frontal pole cortex, dorsolateral PFC, orbitofrontal cortex, and the ACC
Rutter et al. (2013)	θ : 4–8 α : 8–14 β : 14–30 γ : 30–80	<ul style="list-style-type: none"> Coherence Graph theory Source-space estimation using SAM beamforming 4 min eyes-closed 	<ul style="list-style-type: none"> 20 SZ 14 males Mean age: 31.2 ± 10.9 	<ul style="list-style-type: none"> 20 controls 14 males Mean age: 31.3 ± 10.8 	<ul style="list-style-type: none"> \uparrow SMI values compared to controls in rostral PFC for short-range connections \downarrow connectivity for long-range connections to lateral PFC \downarrow PLV overall compared to controls The α spectral band had the highest PL values The largest PLV difference was in the right frontal region
Bowyer et al. (2015)	3–50	<ul style="list-style-type: none"> Coherence Source-space estimation using ICA, MR-FOCUSS 10 min eyes-open 	<ul style="list-style-type: none"> 12 SZ 10 males Mean age: 32 ± 8.8 	<ul style="list-style-type: none"> 12 controls males Mean age: 27 ± 6.5 	<ul style="list-style-type: none"> \uparrow SMI values compared to controls in rostral PFC for short-range connections \downarrow connectivity for long-range connections to lateral PFC \downarrow PLV overall compared to controls The α spectral band had the highest PL values The largest PLV difference was in the right frontal region
Robinson and Mandell (2015)	n/a	<ul style="list-style-type: none"> Symbolic mutual information (SMI) Source-space 	<ul style="list-style-type: none"> 15 SZ 10 males Age range: 20–45 	<ul style="list-style-type: none"> 14 controls 5 males, Age-range: 19–36 	<ul style="list-style-type: none"> \uparrow SMI values compared to controls in rostral PFC for short-range connections \downarrow connectivity for long-range connections to lateral PFC \downarrow PLV overall compared to controls The α spectral band had the highest PL values The largest PLV difference was in the right frontal region
Zhang et al. (2015)	δ : 1–4 θ : 4–8 α : 8–12 β : 12–30 γ : 30–50	<ul style="list-style-type: none"> Phase-lag value (PLV) Sensor-space 4 min eyes-open 	<ul style="list-style-type: none"> 14 SZ Mean age: 27.6 years 	<ul style="list-style-type: none"> 22 controls Mean age: 27.6 years 	<ul style="list-style-type: none"> \uparrow correlation within the dorsal ACC/superior frontal areas, \uparrow between frontal brain areas and perisylvian regions in SZ, \downarrow correlation within the PCC/precuneus region, compared to controls, across all frequency bands In β, \uparrow between the frontal lobe and cerebellum, the frontal lobe and the DMN, and the frontal and auditory networks
Houck et al. (2017)	δ : 1–4 θ : 5–9 α : 10–15 β : 16–29	<ul style="list-style-type: none"> Zero-lag cross-correlations Source-space estimation using beamformer and group spatial ICA 6 min eyes-open 	<ul style="list-style-type: none"> 44 SZ 37 males Mean age: 37.3 ± 13.9 	<ul style="list-style-type: none"> 47 controls 34 males Mean age: 35.2 ± 11.8 	<ul style="list-style-type: none"> \uparrow correlation within the dorsal ACC/superior frontal areas, \uparrow between frontal brain areas and perisylvian regions in SZ, \downarrow correlation within the PCC/precuneus region, compared to controls, across all frequency bands In β, \uparrow between the frontal lobe and cerebellum, the frontal lobe and the DMN, and the frontal and auditory networks

possible that different generators are involved, and that the amplitude and/or peak frequency of delta oscillations differ between healthy and SZ populations (Rockstroh et al., 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).

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; Nolte et al., 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 (0.5–8 Hz), and right occipital and right parietal area in 1–4 Hz (Zhang et al., 2015).

Houck et al. (2017) 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 Mandell (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 salience 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, salience) and sensory areas (visual, auditory). In turn, these appear to be reflective of patients' positive and negative symptoms, possibly due to faulty information processing. Fig. 1 illustrates the above RS MEG findings on connectivity alterations in SZ (specifically synchronizations between a brain region and the rest of the brain).

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 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., 2017). With respect to sample size, Zhang et al. (2015), Robinson and Mandell (2015) and Bowyer et al. (2015) were 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 observed altered connectivity patterns.

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.

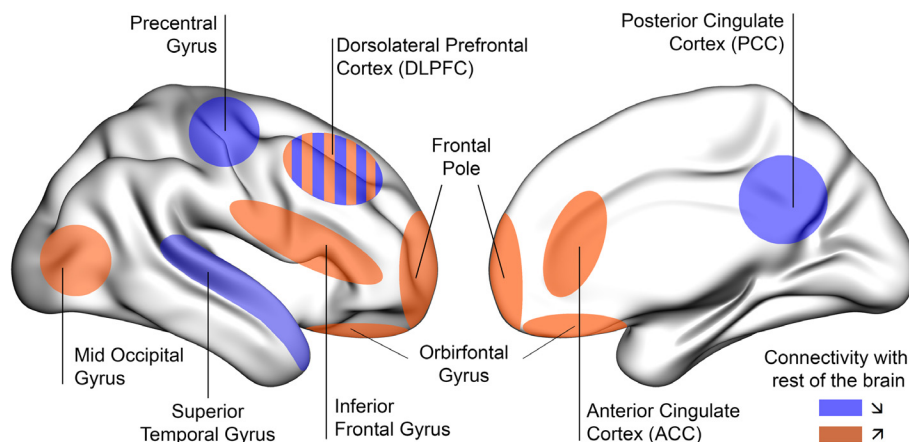


Fig. 1. Schematic overview of the key brain regions that show abnormal connectivity patterns in subjects with schizophrenia (SZ). Here, we show areas for which there is resting-state MEG evidence indicating that these areas have atypical long-range connections with the rest of the brain in patients compared 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The correlational findings between pathological symptoms and connectivity patterns observed in most of the reviewed literature (e.g. Fehr et al., 2001; Sperling et al., 2002; Hinkley et al., 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.

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.

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.

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.

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., 2015). 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.

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., 2017). 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., 2017). 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. Assessing the precision of source-reconstructed MEG data is challenging. While intracranial EEG measurements does offer some access to the ground truth of oscillatory and long-range interactions dynamics (e.g., Ko et al., 2013; Jung et al., 2010; Jerbi et al., 2009; Bastin et al., 2012, 2017; Lachaux et al., 2007), it only pro-

vides limited or indirect support for the non-invasive study of network alterations in psychiatry.

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 min. 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).

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.

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., 2017). 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., 2016), 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., 2017), and EEG (e.g., Kikuchi et al., 2011; Andreou et al., 2014; Ramyeed 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).

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.

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.

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., 2011a,b; 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).

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 min 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 it is possible to combine MEG and EEG using simultaneous acquisition (e.g. Dale and Sereno, 1993; Dubarry et al., 2014; Gavaret et al., 2016; Papadelis et al., 2016; Puce and Hämäläinen, 2017). 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.

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.

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., 2017; 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.

Competing interests

None declared.

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