

REVIEW

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# Electrophysiological insights into connectivity anomalies in schizophrenia: a systematic review

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## Abstract

The pathophysiology of schizophrenia may fundamentally involve a disturbance in the interaction between neuronal groups that leads to impaired communication within and between brain areas. Such a “dysconnectivity syndrome” could underlie the pronounced cognitive deficits as well as the emergence of psychosis. Evidence for this hypothesis has mainly come from functional magnetic resonance imaging (fMRI) studies which have investigated connectivity anomalies during spontaneous as well as task-related activity. In the current review, we will summarize evidence from electro- and magnetoencephalography (EEG/MEG) which have employed measures, such as coherence, phase-locking and mutual information, that have tested changes in functional connectivity during task-related as well as resting-state time-frequency data. We will highlight the methodological issues associated with these measures as well as provide recommendations for future research.

**Keywords:** Schizophrenia, Dysconnectivity, Functional connectivity, Neural synchrony, EEG, MEG

## Background: schizophrenia and neuronal communication

Schizophrenia (ScZ) is a severe mental disorder characterised by psychotic symptoms and cognitive deficits [1–3]. Cognitive and developmental abnormalities are present in both ScZ-patients [4] and their unaffected siblings [5], suggesting that a combination of shared genetic and environmental risk factors leads to aberrant brain maturation. It is estimated that ScZ affects about 1 % of the population, with a considerable impact on the psychosocial functioning and quality of life [6, 7].

The development of modern structural and functional neuroimaging techniques has highlighted the contribution of aberrant organization and functionality of large-scale networks towards the manifestation of clinical symptoms and cognitive disturbances in ScZ [8]. However, a mechanistic understanding of such anomalies as well as the identification of neuroimaging-biomarkers that could aid early intervention and diagnosis has remained elusive. To address these fundamental questions, it is likely that ScZ-research could benefit from an approach that focuses on the dynamic interactions between multiple regions and neural networks at realistic timescale using advanced Electro/Magnetoencephalography (EEG/MEG). This is because it is now clear that cognition is a complex phenomenon stemming from a spatially and temporally precise

flow of information between and within multiple brain regions [9]. Accordingly, focal anatomical and functional alterations in ScZ may only provide partial insights into the neural origins of the disorder, as the clinical symptoms and cognitive deficits are more likely to stem from a *dysconnectivity syndrome* whose main feature is an altered communication between brain regions [10–12].

This approach has gained support from recent work which has highlighted that precise temporal correlations are a prerequisite for efficient neuronal communication in large-scale networks [13, 14]. Emerging evidence suggests that ScZ is associated with alterations in the amplitude and synchrony of rhythms at low- and high-frequencies which could provide a parsimonious mechanisms for the explanation of cognitive deficits and psychosis [15]. Moreover, insights into the rhythm-generating mechanisms underlying neural oscillations and their synchronization across larger areas has identified the contribution of distinct cell-types and transmitter-systems which could establish important links with pre-clinical research that could guide the development of novel treatments [15].

**Functional connectivity in EEG/MEG-data: methodological aspects**

While these data provide preliminary support for the notion that ScZ may involve an impairment in neural synchrony, one impediment towards a better understanding of impaired neuronal communication in ScZ is the availability, implementation and interpretation of measures which allow the analysis of connectivity-parameters in EEG/MEG-data. This issue is crucial since modulations in the amplitude of spectral signals do not per se allow insights into the efficacy of information transmission between neuronal groups. For this to occur, measures of functional interactions need to be implemented. These measures, however, face several methodological challenges.

On a general note, measures of functional connectivity (see Table 1) detect statistical relationships between neural signals over time and thus potentially allow conclusions in

**Table 1** EEG/MEG Measures of functional and effective connectivity

Measure	Description	Altered in ScZ
Coherence	A measure of covariation in the amplitude and/or phase of two neural signals [16]	●●
Imaginary Part of Coherence	An estimate of coherence that focuses on time-lagged synchronization [58]	
Phase-Locking Value	A measures of the covariation in the phase of two neural signals [18]	●●
Phase-Lag Index	A measure of the asymmetry of the distribution of phase differences between two signals [59].	
Granger Causality	Estimates the direction of neural communication between two time-series through predicting the course of activation in another cortical area [60]	●
Transfer Entropy	A method to estimate directed interactions without a priori specification of a model for the data [61]	
Directed Transfer Function	Comparable method to Granger Causality, but normalized for inflow from all areas [60]	●
Mutual Information	Estimation of amount of signal in first area explained by the signal in the second area [62]	●
Synchronization Likelihood	Normalized strength of mutual information between signals from two areas [63]	●

●Preliminary evidence ●●Robust Evidence

regards to the functional interactions between two brain regions. In EEG/MEG-data, the usual starting point for such an approach is first the decomposition of the frequency content of the signal into band-limited spectral values. Traditionally, EEG-data have been examined for changes in coherence between electrodes, where coherences can be defined as the covariation in amplitude and phase between two signals [16]. An important limitation of coherence-measures of scalp EEG/MEG-data are the problem of field spread as sensor-level data represents mixed signals from multiple sources, volume conduction-induced blurring effects, artifact contamination and potential bridging between electrodes in EEG recordings. Moreover, coherence values can be influenced by power fluctuations between two recordings sites, especially if a common source leads to volume conduction across extended areas [17]. Therefore, as an alternative to traditional amplitude-based measures of coherence, more robust measures of phase-locking have been developed, such as the phase-slope index, phase-lag index and imaginary coherence [18, 19]. While these approaches may provide a more sensitive index for the assessment of synchronization between two recording sites than coherence measures, volume conduction effects may still confound such measures [20, 21].

Importantly, because of their correlational nature, functional connectivity measures do not provide direct information on specific neural interactions and can be affected by spurious relationships between signals, e.g. activity in two regions can be highly correlated even in the absence of a direct communication between them if they are both connected with a third common area [22]. On a more complex level, effective connectivity measures, such as Granger Causality and Directed Transfer Functions, describe the direct interactions between neural assemblies, specifying the direction of information transmission.

The recent development of source connectivity analysis has made it possible to at least partially overcome the traditional problem of field spread/volume conduction and to obtain more precise localization of EEG/MEG-activity [23]. Thus, the adoption of functional connectivity measures, especially at the source level, may have considerable potential for investigating dysconnectivity anomalies in schizophrenia. In the following sections we will review the main findings on functional connectivity abnormalities in the time-frequency domain in the disorder. To this end, we selected studies based on a literature search in PubMed with the following search terms: “schizophrenia”, “EEG”, “MEG”, “oscillations”, “synchrony”, “long-range synchrony”, “functional connectivity”, “effective connectivity”, “long-range connectivity”, “coherence”, “phase locking”, “phase synchrony”, “DCM”. Studies with sample sizes < 15 participants as well as reports that analysed only a narrowly defined frequency bin of 1 Hz were excluded. Moreover, studies in which EEG/MEG were combined with neuro-stimulation/modulation techniques were not considered.

### **EEG resting-state connectivity-findings in schizophrenia**

Neural oscillations, especially at alpha-frequencies, are a prominent feature of resting-state activity. Recent MEG-studies of amplitude correlations have revealed resting-state networks similar to those disclosed by Functional Magnetic Resonance Imaging (fMRI) [24, 25].

A large body of work suggests that the resting-state spectral profile in ScZ involves an increase in power at lower (delta 0–4 Hz, and theta 4–7 Hz) frequencies [26]. These

data are complemented by increased connectivity values [27, 28] which correlate with decreased cognitive performance [29]. However, the opposite pattern of reduced delta/theta-band coherence was observed in some studies as well [30–32]. One possibility is that abnormalities in low-frequency connectivity patterns involve regionally specific changes. For example, one study showed that while intra-hemispheric delta-coherence was increased, inter-hemispheric coherence values showed the opposite pattern in ScZ-patients relative to controls [30].

The majority of studies that examined connectivity-measures at alpha-frequencies reported a decrease in ScZ. In particular, decreased alpha-connectivity, as expressed by coherence values as well as lagged coherence and phase synchrony, has been reported at frontal [27, 31], fronto-posterior [27, 28] and parieto-temporal [27] regions (for different findings see [29, 30, 32, 33]). Interestingly, two studies reported a correlation between alpha connectivity at rest and symptom dimension in ScZ [33, 34].

There is conflicting evidence regarding alterations in fast oscillations at beta- (13–30 Hz) and gamma- (30–200 Hz) band frequencies at rest, with evidence for both elevated [27], reduced [30] and intact [28, 29, 31, 32] beta-band connectivity. Preliminary evidence suggests that beta-band coherence is influenced by illness progression and clinical symptoms [27]. One study examining the relationship between lagged phase synchrony (LPS) and cortical distance showed a more pronounced decrease of beta 1 (13–21Hz) LPS with increasing cortical distance in first-episode psychosis patients (FEP) compared to healthy controls, while opposite findings were obtained for the beta 2 (21–30 Hz) band [35]. Similar results in the beta 1 band have been obtained in at-risk subjects who will later develop psychosis [36].

Similar conflicting findings have been reported on measures of gamma-band connectivity, with two studies reporting no difference with controls [30, 32], and one study reporting increases in ScZ-patients with a recent onset and decreases in patients with prolonged illness compared to controls [27]. However, the effect of illness duration is still unclear, since both increases [37] and no differences [28, 29] in gamma-band connectivity measures have been observed in FEP relative to healthy subjects (Table 2).

**EEG/MEG parameters during task-related activity in schizophrenia**

Neuronal communication through synchronized, rhythmic activity has been proposed to underlie the emergence of cognitive functions and behaviour [13, 14]. Accordingly, correlations can be expected between alterations in cognitive and perceptual processes

**Table 2** Summary of findings on resting-state connectivity in ScZ

Authors	Technique	Measure	$\delta$	$\Theta$	$\alpha$	$\beta$	$\gamma$
Andreou et al. [29]	EEG	Source-space Imaginary Coherence	=	▲	=	=	=
Andreou et al. [37]	EEG	Source-space Power-envelope Correlation	-	-	-	-	▲
Di Lorenzo et al. [27]	EEG	Source-space Lagged Phase Synchrony	▲	▲	▼	▲	▲▼
Hinkley et al. [33]	MEG	Global Connectivity	-	-	▲▼	-	-
Kam et al. [30]	EEG	Coherence	▲▼	▼	▲	▼	=
Lehmann et al. [28]	EEG	Source-based Lagged Coherence	▲	=	▼	=	=
Tauscher et al. [31]	EEG	Coherence	▼	▼	▼	=	-
Winterer et al. [32]	EEG	Coherence	▼	▼	=	=	=

▲Increase, ▼Decrease, = not altered connectivity, – not reported/investigated

and changes in EEG/MEG parameters that allow the quantification of interactions between sensor/source-estimates of rhythmic activity.

Several investigations into the possible role of alterations in coherence and synchrony during auditory perception have been conducted, in particular using the Auditory Steady State Paradigm (ASSR). Steady-state responses (SSRs) are evoked oscillatory responses that are entrained to the frequency and phase of temporally modulated stimuli, providing information about the integrity of sensory and perceptual pathways. Alterations in SSRs have been widely documented in ScZ [38], but only few studies investigated connectivity patterns during ASSR. During 40 Hz ASSRs, decreased phase synchrony between left and right primary auditory cortices has been observed in ScZ [39]. Similarly, decreased fronto-temporal coherence during an auditory oddball task has been observed in ScZ-patients and their siblings [40]. Interestingly, there is preliminary evidence that abnormal interhemispheric alpha coherence during auditory processing may be related to the severity of auditory hallucinations [41], suggesting that aberrant patterns of neuronal communication may also be involved in the positive symptoms of ScZ.

During visual processing, previous studies have focused on the possibility that long-range synchronization during perceptual integration may be impaired at beta/gamma-band frequencies. Two studies [42, 43] reported a reduction of phase-synchronization during visual processing requiring perceptual binding along different stages of the visual hierarchy. Alterations in fronto-posterior high-frequency connectivity in ScZ have been also reported during smooth pursuit eye movements [44], a reliable endophenotype of ScZ. Furthermore, alterations in alpha connectivity have been related to impaired recognition of facial emotional expression in ScZ [45]. Together these findings suggest that abnormal functional interactions as identified by altered coherence and phase-synchronization could be involved in both basic visuo-perceptual deficits and as well contribute to higher cognitive impairments in ScZ.

Finally, there is preliminary evidence on alterations in connectivity changes during higher cognitive functions, such as working memory (WM). Neural synchrony has been proposed as a mechanism for facilitating mnemonic processes [46], and specifically, theta synchrony has been related to retention [47] and central executive processes underlying WM [48]. In line with the dysconnectivity hypothesis, decreased fronto-parietal theta phase synchrony was associated with impaired performance in a visual WM task in ScZ-patients [49] (Table 3).

## Discussion

The current overview highlights the possibility of impaired functional connectivity at different frequencies in ScZ. Given the potential importance of aberrant neuronal communication towards the emergence of cognitive deficits and clinical symptoms [10–12], we believe it is important to pursue this approach further albeit considering several methodological and conceptual caveats for the analysis and interpretation of functional connectivity measures in EEG/MEG-data.

This is particularly the case for resting-state measurements which currently provide conflicting evidence for the presence and direction of effects in functional connectivity parameters of rhythmic activity in ScZ. Similarly to coherence and phase-synchrony estimates during task-related oscillations, volume conduction effects can lead to spurious

**Table 3** Summary of findings on task-related connectivity in ScZ

Function	Authors	Technique	Measure	Increase/decrease
Auditory Processing	Henshall et al. [41]	EEG	Coherence	▼ $\alpha$
Auditory Processing	Mulert et al. [39]	EEG	Source-space Lagged Phase synchrony	▼ $\gamma$
Auditory Processing	Winterer et al. [40]	EEG	Coherence	▼ $\delta$
Face Processing	Lee et al. [42]	EEG	Event-Related Phase Coherence	▼ $\gamma$
Face Processing	Uhlhaas et al. [43]	EEG	Phase Synchrony	▼ $\beta$
Smooth Pursuit Eye Movement	Krishna et al. [44]	EEG	Phase Synchrony	▼ $\beta \gamma$
Facial Emotional Processing	Popov et al. [45]	MEG	Graph-based Index of Global Connectivity	▲ ▼ $\alpha$
Working Memory	Griesmayr et al. [49]	EEG	Phase-Locking Value	▼ $\Theta$

▲ Increase, ▼ Decrease, = intact connectivity

correlations between EEG/MEG-sensor estimates for resting-state measurements [17]. This may be particularly the case in scenarios where the spectral content of time-frequency data is already different between clinical and non-clinical populations and thus lead to biased estimates of connectivity parameters that do not reflect “true” alterations in the interaction between neuronal channels but rather the impact of widely different spectra.

One solution to this problem is the transformation of EEG/MEG-data into source-space which allows the reconstruction of the underlying generators which can then be further interrogated for connectivity parameters. Difficulties with this approach are the limited spatial resolution which can impede the separation of sources in nearby brain regions as well as similar contributions of volume conduction towards phase-estimates, for example, of time-series data. Recent approaches towards this problem have seen the removal of signals with zero-phase lag through orthogonalization [25] as well as the investigation of power-correlations of EEG/MEG source-reconstructed signals [50]. However, such approaches are still yet to be applied to ScZ research (see [51–53] for findings in Dementia and Epilepsy).

In addition, future research should also carefully consider the analysis of connectivity parameters of high-frequency activity at rest. Recent findings have highlighted the importance of careful artefact removal from EEG/MEG-recordings to diminish the influence of cranial and muscle activity towards estimates of beta/gamma-band activity [54]. Although MEG-data is faced with similar problems as in EEG-recordings [55], there is evidence to suggest that EEG may be characterized by reduced signal-to-noise for estimating gamma-band fluctuations [56]. This is a particular pertinent issue in measuring high-frequency activity during spontaneous activity because of the small contribution of beta/gamma-band fluctuations towards the measured EEG/MEG-signal which makes the separation of gamma-band activity due to neural vs. non-neural activity particularly challenging. While this problem has been mainly addressed in the context of time-frequency analysis of EEG/MEG-data, we would like to note that it is likely that the contamination of electrophysiological signals through cranial and muscle artefacts can also lead to spurious correlations between EEG/MEG signals. There is emerging evidence that the contribution of such artefacts towards resting-state connectivity estimates at frequencies > 30 Hz may be higher in EEG-data [50].

While the current findings of task-related rhythmic activity in ScZ are slightly more consistent than data from resting-state activity in highlighting a reduced functional coupling between brain areas, we would like to highlight that similar methodological issues also apply to the analysis of connectivity parameters during cognitive and perceptual paradigms which, in our view, have been insufficiently addressed. One advantage of analysis of task-related rhythmic activity is that stimulus-induced oscillations lead to higher changes in the spectral content of EEG/MEG-data than ongoing-spontaneous oscillations which facilitates the separation of artefacts from signals due to neural processes, especially if baseline or pre-stimulus activity is subtracted from post-stimulus activity.

A potential caveat for the analysis of connectivity-parameters during task-related EEG/MEG-data is, however, that stimuli that are associated with large transient activity as is the case during visual and auditory paradigms, can lead to spurious correlations between sensor/source-signals. This is less the case where task-related activity predominantly involves intrinsic oscillations which occur during higher cognitive processes, such as attention, memory and executive processes [57]. To improve the ability to identify “true” neuronal interactions from EEG/MEG-data, analysis should focus on frequencies that show distinct peaks in the time-frequency content of the signal that point towards task-related modulation of ongoing rhythmic activity. Further investigation of such distinct peaks with connectivity estimates may then allow physiologically meaningful insights into the structure of neuronal communication and its disturbances in ScZ. Given the difficulties of identifying such patterns from EEG/MEG sensor-data, we believe that future studies should preferentially employ such analysis at the source-level.

## Conclusions

We believe that a focus on identifying aberrant patterns of neuronal communication in EEG/MEG-data has considerable potential for ScZ-research. The current evidence suggests that such abnormalities are present in functional connectivity indexes both during resting-state and task-related activity across different frequencies with considerable inconsistencies in terms of the direction of effects. As a result, for these approaches to be useful measures for early intervention and development of biomarkers, the methodological issues raised need to be addressed as well as standardized protocols should be implemented to facilitate replicability across samples.

## Abbreviations

ASSR: Auditory steady state paradigm; DCM: Dynamic causal modelling; EEG: Electroencephalography; FEP: First episode psychosis; fMRI: Functional magnetic resonance imaging; Hz: Hertz; LPS: Lagged phase synchrony; MEG: Magnetoencephalography; ScZ: Schizophrenia; SSR: Steady-state response; UHR: Ultra-high risk for psychosis; WM: Working memory

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## Authors' contributions

All authors contributed equally to this work. All authors read and approved the final manuscript.

## Competing interests

The authors declare that they have no competing interests.

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