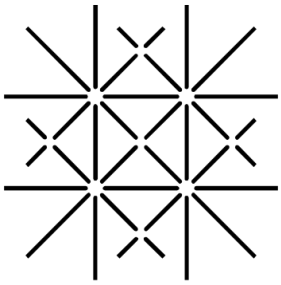

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Predicting Psychosis in At-Risk Patients using Abnormal Neural Oscillations and Synchrony in Conjunctions with Machine Learning Algorithms

A Cumulative Dissertation

Submitted to the Faculty of Psychology, University of Basel,

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

by

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From Vancouver, Canada

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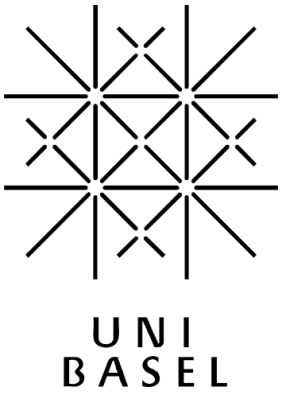

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Life is like riding a bicycle.

To keep your balance, you must keep moving.

-Albert Einstein

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Abstract

In the last 20 years, there has been a marked increase in interest in the early detection and treatment of psychosis. Despite the various potential "prodromes" that have been identified and have helped to increase the accuracy in the detection of persons at-risk of developing psychoses, it is still not possible to predict the transition to psychosis with sufficient accuracy. Although some electroencephalography (EEG) studies, based on basic power-spectral and event-related potential analyses, have been conducted in the field of early detection, neural oscillations and their phase-synchronization across brain areas have been ignored.

The present dissertation covers three different studies which, together, demonstrate that neural oscillations are disturbed in emerging psychosis. The first paper shows that at-risk patients with later transition to psychosis are characterized by abnormal localized brain activity and that inter-cortical areas of the brain are poorly synchronized. The second study shows that machine learning algorithms can detect patterns of abnormal brain activity predictive of later transitions to psychosis with promising accuracy. The third study reveals, in a cross-sectional manner, that patients who already had a first episode of psychosis at inclusion, already demonstrated the same abnormal patterns of brain activity revealed in at-risk patients with later transition to psychosis.

Abbreviations

AUC:	area under the curve
ARMS:	at-risk mental state for psychosis
ARMS-T:	at-risk mental state for psychosis with later transition to psychosis
ARMS-NT:	at-risk mental state for psychosis without later transition to psychosis
BA:	Brodmann area
BPRS:	brief psychiatric rating scale
CSD:	current-source density
EEG:	electroencephalography
FEP:	first episode of psychosis
FePsy:	Früherkennung von Psychosen
fMRI:	functional magnetic resonance imaging
HC:	healthy controls
LASSO:	least absolute shrinkage and selection operator
LORETA:	low-resolution brain electromagnetic tomography
MRI:	magnetic resonance imaging
LPS:	lagged phase synchronization
ROI:	region of interest

Introduction

Early Detection of Psychosis

Over the past decade, there has been an increased awareness of the potential clinical benefits of early recognition and treatment of psychosis. During this time, many early detection clinics have been established worldwide. This development has been triggered in the wake of the following observations:

Schizophrenia is typically predated by prodromal symptoms, which can sometimes be observed as early as in childhood (McGorry et al. 1996; Riecher-Rössler et al. 2006). Schizophrenic psychoses are increasingly acknowledged as neurodevelopmental disorders (Insel 2010; Murray et al. 2004; Waddington 1993; Weinberger 1987).

There is a significant delay between the first prodromal symptoms and its diagnosis which ranges from 4 to 5 years (Riecher-Rössler et al. 2006). Additionally, it has also been shown that a significant delay between the first psychotic symptoms of the illness and its diagnosis, leading to the so-called duration of untreated psychosis (DUP), ranges from 1 to 3 years on average (Marshall et al. 2005; Riecher-Rössler et al. 2006). A longer DUP has been associated with worse functional outcomes, increased risk of drug abuse, decreased autonomy (Perkins et al. 2005; van Os et al. 2009), greater loss of grey matter volume (Borgwardt et al. 2008), more cognitive deterioration (Amminger et al. 2002), higher dosage of neuroleptics (McGorry et al. 1996) and higher overall treatment costs (Moscarelli 1994; for review, see Riecher-Rössler et al. 2006). By contrast, an early psychological or pharmacological treatment can considerably improve the prognosis of the patients (Amminger et al. 2010; Phillips et al. 2007; Woods et al. 2007).

In the light of the above observations, an essential goal of early detection programs is to identify as accurately and as early as possible the individuals who would develop a full-

blown psychosis. This detection allows for an early intervention, thereby reducing the chances of a transition to frank psychosis, which typically occurs during a life period that is critical for education and building up of social networks (van Os et al. 2009). Specifically, worldwide research efforts over the past two decades have developed four main sets of clinical criteria for prospective identification of individuals exhibiting a prodromal syndrome indicative of increased risk for developing a full-blown psychotic illness: Attenuated Psychotic Symptoms (APS), Basic Symptoms (BS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), Genetic Risk and Deterioration syndrome (GRD) and Unspecified Prodromal Symptoms (UPS) (for a detailed description of these criteria and their assessment, see (Fusar-Poli et al. 2013)). Those who meet these criteria are termed “Ultra High Risk (UHR)”, “Clinical High Risk (CHR)” or “At-Risk Mental State (ARMS)” patients (Fusar-Poli et al. 2012b). For this thesis, the term ARMS will be employed to highlight that these individuals are not only at-risk of transitioning to frank psychosis, but are also already in a state in which they manifest some symptoms. Following identification as clinically at risk, these individuals have a risk of developing frank psychosis of about 18% within the initial 6 months, 22% within one year, 29% within two years and 32 % within three years (Cannon et al. 2008; Fusar-Poli et al. 2012b). While several risk factors have served to predict the conversion to psychosis among ARMS individuals, namely, the patient’s age (Fusar-Poli et al. 2012b), deficiencies in cognitive functioning (Fusar-Poli et al. 2012a), alterations in the brain structure (Cannon et al. 2015; Fusar-Poli et al. 2012b; Fusar-Poli et al. 2012c), brain function (Fusar-Poli et al. 2012a; Fusar-Poli et al. 2012b) and neurochemistry (Fusar-Poli et al. 2007; Smieskova et al. 2010), it is still not possible to predict conversion to psychosis with adequate accuracy to justify early interventions, particularly with medications that are associated with potential side effects or long-term medical risks (Ruhrmann et al. 2012).

Among the most encouraging approaches to address the problem of early detection of risk of psychosis is the investigation of neurocognitive impairments. These impairments form a fundamental feature of schizophrenia (Kahn et al. 2013) and occur across various cognitive domains, including working memory, attention, verbal/visual learning and memory, problem solving and social cognition (Keefe et al. 2012). Among the most disturbed domains is working memory (Forbes et al. 2009; Zanello et al. 2009), which is defined as the mental activity of dynamically processing multiple pieces of information from various sensory modalities during reasoning and comprehension (Becker et al. 1999). Another key impairment of those affected by schizophrenia is social cognition; these patients perform poorly when trying to infer other people's feelings or intentions (theory of mind) (Corcoran et al. 1995; Tan et al. 2005) and were shown to have difficulties interpreting simple facial expressions such as a smile or an angry face (Corcoran et al. 1995).

Studies have revealed that cognitive impairments are not only present in schizophrenic psychoses; they are also observed in ARMS individuals, albeit to a lower extent (Fusar-Poli et al. 2012a; Pflueger et al. 2007). In addition, ARMS individuals who later on developed psychosis (ARMS-T) already at baseline, i.e. when they first sought help, had more severe neurocognitive deficits than those who did not make a transition later on (ARMS-NT) (De Herdt et al. 2013; Fusar-Poli et al. 2012a; Riecher-Rössler et al. 2006; Seidman et al. 2010). In line with these results, studies have revealed that neurocognitive measurements could considerably enhance the prediction of psychosis (Koutsouleris et al. 2012b; Riecher-Rössler et al. 2009; Seidman et al. 2010). Furthermore, these measurements also yield a good prediction of the functional outcome of the illness as they are considered to be key contributors to the pathophysiology of schizophrenia (Green 1996; Green et al. 2004). Even though

cognitive impairments at the onset of psychosis have been assessed by means of behavioural measurements, their neural underpinnings as measured by neurophysiological and/or neuroimaging tools such as electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) are relatively less studied. These neuroscientific tools allow direct assessment of the neural aberrations that, when taken together, appear to precede full blown schizophrenic psychoses.

Event-Related Potentials

Most of the EEG studies conducted on ARMS individuals have assessed event-related potentials (ERP). Among the most studied ERP paradigms are the mismatch negativity (MMN) paradigm, the oddball P300 paradigm and the P50 sensory gating paradigm. MMN is an ERP component induced by a deviant tone that is presented within a series of repeated standard tones. It has been shown that repeated standard tones prompt a prediction for the following tone. In other words, through processing a series of repeated tones, a context for the processing of subsequent auditory stimuli is generated. Thus, each time a tone deviates from this "context", a prediction error is generated, which is reflected in the MMN as measured by EEG (Garrido et al. 2008; Schmidt et al. 2013). Several studies have shown that ARMS individuals who later convert to psychosis demonstrated reduced MMN at frontal electrodes when compared to non-converters and healthy controls (HC)(Bodatsch et al. 2015).

An additional task that yielded promising results is the oddball P300 ERP paradigm. In the auditory version of this paradigm, participants are asked to respond (button press or counting) to an infrequent auditory target stimulus randomly imbedded in a series of frequent standard auditory stimuli. The anticipation of the repeated standard stimulus generates a context, while the target stimulus generates a positive voltage ERP

component at about 300 ms post-stimulus known as the P300 or P3b. The P300 has been linked to context-updating of working memory and to allocation of attentional resources to processing an infrequent task-relevant target stimulus (Donchin et al. 1988; Mathalon et al. 2000; Polich et al. 1995). Using this task, it has been shown that ARMS individuals have a reduced parietal P3b (van Tricht et al. 2010) and that the extent of this reduction is predictive for subsequent psychosis in ARMS individuals (van Tricht et al. 2010). Together, these studies suggest that ARMS individuals have deficits in auditory sensory echoic memory and predictive coding (MMN) as well as in auditory attention and contextual updating of working memory (P300). Both are indicative of a heightened risk for full blown psychosis and are possibly contributory to the transition to full blown psychosis. These neurophysiological abnormalities may further underlie or contribute to cognitive deficits in psychosis (Barch et al. 2012). As a whole, these findings provide evidence that ERPs could be exploited to predict which ARMS individuals are at greatest risk for conversion to a psychotic disorder.

Spontaneous Neuronal Oscillations

An alternate approach in clinical EEG research has been the investigation of the surface-power of spontaneous neuronal oscillations at different frequency bands during resting state. Neural oscillations are fundamental mechanisms for the coordination and synchronisation of neural responses in the cortex (Mathalon et al. 2015; Ward 2003). These oscillations are the direct reflections of the brain's rhythm-generating networks of interneurons and cortico-cortical connections (see Mathalon et al. 2015; Uhlhaas et al. 2010 for review). Using power spectral analyses based on quantitative EEG (qEEG), converging evidence indicates that patients with schizophrenia are characterized by increased low-frequency power and diminished alpha-band (Sponheim et al. 2000), and attenuated gamma power in response to task stimuli (Perez et al. 2013; Roach et al.

2008; Uhlhaas et al. 2010). Additionally, it has also been shown that negative symptoms are associated with low frequencies (theta and delta bands) in patients with a first episode of psychosis (FEP) (Gschwandtner et al. 2009). Finally, the combination of the amount of power with negative symptoms has been shown to improve the prediction of psychosis (Zimmermann et al. 2010). In a recent study, Ramyead and colleagues have demonstrated that ARMS-T exhibited increased gamma activity in the medial prefrontal cortex during resting EEG that was strongly associated with non-verbal cognitive capabilities. These individuals also seemed to show disrupted inter-cortical beta phase synchronization that worsened in association with increasing psychotic symptoms (Ramyead et al. 2014).

Prediction of Psychosis using Multivariate Approaches

Some studies have shown that ARMS individuals who later convert to psychosis have more pronounced abnormalities in brain structure and activity (Borgwardt et al. 2008; Borgwardt et al. 2007; Cannon et al. 2015; Fusar-Poli et al. 2012a; Fusar-Poli et al. 2012c; Perez et al. 2014; van Tricht et al. 2010). Nonetheless, these studies mostly made use of univariate approaches (such as ANOVAs), did not aim at individualized prediction and did not cross-validate their prediction, as has been strongly recommended by methodologists (Steyerberg 2008). However, in two recent studies, Koutsouleris and colleagues applied multivariate pattern recognition techniques to neuroanatomical and neuropsychological data with promising results (Koutsouleris et al. 2012a; Koutsouleris et al. 2014). In a recent study, I have demonstrated that machine-learning algorithms could be applied to clinical EEG data also with promising results (Ramyead et al. 2015)

Published Original Research Papers

Avinash Ramyead, Erich Studerus, Michael Kometer, Martina Uttinger, Ute Gschwandtner, Peter Fuhr, Anita Riecher-Rössler: *Prediction of psychosis using neural oscillations and machine learning in neuroleptic-naïve at-risk patients*. The World Journal of Biological Psychiatry 10/2015; DOI:10.3109/15622975.2015.1083614

Avinash Ramyead, Michael Kometer, Erich Studerus, Susan Koranyi, Sarah Ittig, Ute Gschwandtner, Peter Fuhr, Anita Riecher-Rössler: *Aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis*. Schizophrenia Bulletin 09/2014; DOI:10.1093/schbul/sbu134

Andrea Spitz, Erich Studerus, Susan Koranyi, Charlotte Rapp, **Avinash Ramyead**, Sarah Ittig, Ulrike Heitz, Martina Uttinger, Anita Riecher-Rössler: *Correlations between self-rating and observer-rating of psychopathology in at-risk mental state and first-episode psychosis patients: influence of disease stage and gender*. Early Intervention in Psychiatry 10/2015; DOI:10.1111/eip.12270

Martina Uttinger, Susan Koranyi, Martina Papmeyer, Fabienne Fend, Sarah Ittig, Erich Studerus, **Avinash Ramyead,** Andor Simon, Anita Riecher-Rössler: *Early detection of psychosis: helpful or stigmatizing experience? A qualitative study*. Early Intervention in Psychiatry 10/2015; DOI:10.1111/eip.12273

Sarah Ittig, Erich Studerus, Martina Papmeyer, Martina Uttinger, Susan Koranyi, **Avinash Ramyead**, A. Riecher-Rössler: *Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects*. European Psychiatry 12/2014; 30(2). DOI:10.1016/j.eurpsy.2014.11.006

Publication 1: “Aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis“

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Aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis

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Background: **Converging evidence indicates that neural oscillations coordinate activity across brain areas, a process which is seemingly perturbed in schizophrenia. In particular, beta (13-30 Hz) and gamma (30–50 Hz) oscillations were repeatedly found to be disturbed in schizophrenia and linked to clinical symptoms. However, it remains unknown whether abnormalities in current source density (CSD) and lagged phase synchronization of oscillations across distributed regions of the brain already occur in patients with an at-risk mental state (ARMS) for psychosis.** ***Methods:*** **To further elucidate this issue, we assessed resting-state EEG data of 63 ARMS patients and 29 healthy controls (HC). Twenty-three ARMS patients later made a transition to psychosis (ARMS-T) and 40 did not (ARMS-NT). CSD and lagged phase synchronization of neural oscillations across brain areas were assessed using eLORETA and their relationships to neurocognitive deficits and clinical symptoms were analyzed using linear mixed-effects models.** ***Results:*** **ARMS-T patients showed higher gamma activity in the medial prefrontal cortex compared to HC, which was associated with abstract reasoning abilities in ARMS-T. Furthermore, in ARMS-T patients lagged phase synchronization of beta oscillations decreased more over Euclidian distance compared to ARMS-NT and HC. Finally, this steep spatial decrease of phase synchronicity was most pronounced in ARMS-T patients with high positive and negative symptoms scores.** ***Conclusions:*** **These results indicate that patients who will later make the transition to psychosis are characterized by impairments in localized and synchronized neural oscillations providing new insights into the pathophysiological mechanisms of schizophrenic psychoses and may be used to improve the prediction of psychosis.**

Key words: schizophrenia/at-risk mental state (ARMS)/resting state/EEG

Introduction

Converging evidence suggests that an impaired dynamic coordination of activity across distributed brain areas underlies the cognitive and behavioral abnormalities that characterize psychosis.[1–4] Neural oscillations coordinate distributed activity through phase synchronization,[5] and patients with schizophrenia display altered neural oscillations, particularly in the beta (13–30 Hz) and gamma (30–50 Hz) frequency bands.[3,6] Together, these findings suggest that alterations in higher frequency oscillations and their phase synchronization may disrupt coordinated activity across distributed cortical areas, thereby leading to the formation of psychotic symptoms and cognitive impairments.

Gamma oscillations are strongly associated with the integration of cognitive information[7–9] and have been shown to be consistently perturbed in patients with schizophrenia.[3,10,11] Interestingly, both an elevated and reduced gamma activity has been reported in patients with schizophrenia.[12] However, an increase has consistently been found in unmedicated patients experiencing positive symptoms (such as hallucinations and delusions), while the reverse is apparent in those suffering from negative symptoms (such as social withdrawal, lack of motivation, and flat affect).[11,12] Although both gamma and beta oscillations synchronize with enhanced precision over small distances, the beta oscillations have been shown to be particularly important in modulating long-range synchronization,[13,14] which is the interaction among widely distributed neocortical regions. For instance, the phase synchronization of beta oscillations between extra-striate areas[15] and between temporo-parietal areas[16] have been shown to mediate attentional processes. Interestingly, all these processes are deeply perturbed in patients with

schizophrenia,[17–19] further suggesting a disturbed long-ranged neural communication. As a coordinator of these large-network interactions, the beta frequency is therefore a prime candidate to be studied.

Although several EEG studies have been conducted on first episode psychosis (FEP) and chronic schizophrenia patients, studies on prodromal patients are scarce. This is unfortunate because schizophrenia is now increasingly seen as a neurodevelopmental disorder[20] and thus studying neurophysiological abnormalities in at-risk mental state (ARMS) patients would offer a unique opportunity to unravel the etiopathology of the disease.[19] Furthermore, previous studies on ARMS patients[21,22–24] did not make use of electrophysiological neuroimaging methods such as eLORETA which allows a reliable source localization of brain activity along with various connectivity analyses of frequencies.[25] Moreover, studies were frequently based on patients treated with antipsychotic drugs, which could have severely obfuscated the discovery of neurophysiological correlates of psychopathology.[26]

Thus, we compared beta and gamma oscillations in 3 relatively large and antipsychotic-naive groups, ie, ARMS patients with later transition to psychosis (ARMS-T), ARMS patients without later transition to psychosis (ARMS-NT) and healthy controls (HC). We not only assessed the current source density (CSD) at these frequency bands, but also their lagged phase synchronization across brain areas as a function of Euclidian distance. We hypothesized that ARMS-T patients would demonstrate abnormal CSD in both the high gamma and beta frequency bands when compared with ARMS-NT and HC. Furthermore, we postulated that the lagged phase synchronization of beta, the long-range modulator, would be more decreased in ARMS-T compared to ARMS-NT and HC as a function of increasing Euclidian distance.

Methods

Setting and Recruitment

The EEG data analyzed in this study were collected as part of the Basel ***F***rüh***e***rkennung von ***Psy***chosen (***FePsy***) project, a prospective multilevel study, which aims to improve the early detection of psychosis.[27] The study was approved by the ethics committee of the University of Basel, and all participants provided written informed consent. Patients recruited for this study were help-seeking consecutive referrals to the ***FePsy*** Clinic at the University Psychiatric Clinics Basel, which was specifically set up to identify, assess, and treat individuals in the early stages of psychosis.

Screening Procedure

We used the Basel Screening Instrument for Psychosis (BSIP)[28] to identify ARMS individuals. The BSIP is based on the PACE inclusion/exclusion criteria[29] and has been shown to have a high predictive validity and a good interrater reliability.[28] Exclusion criteria for patients were age younger than 18 years, insufficient knowledge of German, IQ < 70, previous episode of schizophrenic psychosis (treated with major tranquilizers for >3 weeks [lifetime] and 125 mg chlorpromazine equivalent/day), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed depression or borderline personality disorder. For this study, we included all ARMS patients that were recruited for the ***FePsy*** study between March 2000 and August 2013 and had a clinical EEG session of at least 15 min at baseline assessment. They were followed-up at regular intervals in order to distinguish those who later transitioned to frank psychosis (ARMS-T) from those who did not (ARMS-NT). During the first year of the follow-up, ARMS individuals were assessed for transition to psychosis monthly, during the second and third years 3-monthly, and thereafter annually using the transition criteria of Yung et al.[29] In this study, individuals were only classified as ARMS-NT if they had a follow-up duration of at least 3 years and did not develop frank psychosis. HC were recruited from trade schools, hospital staff, and through advertisements. Inclusion criteria for the healthy participants were: no history of psychiatric or neurological disease, no past or present substance abuse or head trauma.

EEG Recordings and Data Acquisition

EEG data were recorded at the University Hospital of Basel. Patients sat in a quiet room during eyes closed resting-state condition for about 20 min. Every 3 min, subjects were asked to open their eyes for a period of 5–6 s. At any signs of behavioral and/or EEG drowsiness, the patients were verbally asked to open their eyes. EEG data were sampled at a rate of 250 Hz by 19 gold cup electrodes (Nicolet Biomedical, Inc.) referenced to linked ears. Electrodes impedances were kept below 5Ω.

Artifact Rejection

EEG pre-processing was performed using Brain Vision Analyzer 2.0 software (Brain Products GmbH). We processed each EEG in parallel split into 2 branches, one filtered at 0.5 Hz and one at 1 Hz. We did so in order to apply the ICA matrix from the most stable signal (1 Hz) to the one that conserved the most signal (0.5 Hz). Both branches were handled in the same way up to the step that involved re-referencing to the common average. As a first step, artifact rejection was performed manually, based on visual inspection, to remove epochs containing extreme ocular artifacts, muscles and/or cardiac contamination and bad signals due to random movements. Biased extended Infomax ICA analyses were then performed for the removal of residual eye movements, eye-blinking, muscles and non-biological

components contaminated with high gamma frequencies of 50 Hz and above as measured by Fast Fourier Transform (FFT) of the ICA components (resolution at 1 Hz, power μV^2, hanning window length of 10%). After applying the ICA corrected matrix of the data filtered at 1 Hz to the one filtered at 0.5 Hz, we re-referenced the data to common average. Finally, another manual rejection based on visual inspection was performed to exclude remaining artifacts as mentioned above.

EEG Current Source Localization Density Analysis

To compute the cortical CSD of neural oscillations, we used exact low-resolution electromagnetic tomography (eLORETA)[25] on EEG data segmented into 2s epochs (on average 669 segments per subject). Patient groups did not significantly differ in number of segments. eLORETA is a neurophysiological imaging technique based on a weighted minimum norm inverse solution procedure allowing for the 3D modeling of the EEG CSD with an exact localization performance, but with a high correlation of neural sources that are in close proximity. Numerous studies based on neuroimaging tools, such as functional[30,31] and structural magnetic resonance imagery (MRI),[32] positron emission tomography (PET),[33–35] and intracranial EEG recordings,[36,37] have validated LORETA as an efficient and reliable tool to study brain activity. Compared with the first version of LORETA,[38] eLORETA has no localization bias in the presence of structured noise in simulated data.[39]

In eLORETA, a 3-shell spherical head model (brain, scalp, and skull compartments) is used and the solution space is restricted to the cortical gray matter/hippocampus, which comprises 6239 voxels of 5mm × 5mm × 5mm each. The head model for computing the lead field is based on the Montreal Neurological Institute (MNI) brain MRI average.[40]

Lagged Phase Synchronization Analysis

For a spatially unbiased lagged phase synchronization analysis we defined regions of interests (ROIs) based on the MNI coordinates of the cortical voxel underlying the 19 electrode sites[41] (for technical details, see supplementary appendix 3). We used a single voxel for each ROI because eLORETA's spatial resolution is relatively low, and expanding the ROI to neighboring voxels could potentially bias the analysis due to the high correlation among them.[41] Next, we computed the lagged phase synchronization between all 19 ROIs resulting in a relatively high number (ie, 171) of pairwise combinations. Lagged phase synchronization quantifies the non-linear relationship between 2 ROIs after the instantaneous zero-lag contribution has been removed. Removing this instantaneous zero-lag contribution has been shown to eliminate non-physiological artifacts, such as volume conduction, which biases relationship measurements such as instantaneous connectivity.[25] Finally, we used the statistical software R[42] for calculating the distances between ROIs in 3D in order to asses local vs global phase synchronization. The Euclidian distance between ROI1 (x_1, y_1, z_1) and ROI2 (x_2, y_2, z_2) were calculated using the Pythagorean theorem: $\sqrt{[(x_2-x_1)^2 + (y_2-y_1)^2 + (z_2-z_1)^2]}$ and were subsequently standardized into *z*-scores.

Neurocognitive Assessment

In order to assess the participants' non-verbal capabilities to process and integrate higher-order relationships between individual entities we used the Leistungsprüfsystem Scale 3 (LPS-3), a well-established German intelligence scale for assessing nonverbal (abstract reasoning) abilities.[43] To assess working memory, we used the 2-back task of the Testbatterie zur Aufmerksamkeitsprüfung (TAP).[44]

Assessment of Positive and Negative Psychotic Symptoms

The Brief Psychiatric Rating Scale Expanded (BPRS-E)[45,46] was used to assess positive and negative psychotic symptoms. The positive psychotic symptom scale was based on the 4 items hallucinations, suspiciousness, unusual thought content, and conceptual disorganization and the negative psychotic symptom scale was based on the items blunted affect, psychomotor retardation and emotional withdrawal, as defined by Velligan et al.[47]

Statistical Analyses

In order to identify the CSD differences between groups (ARMS-NT vs HC, ARMS-T vs HC, ARMS-NT vs ARMS-T), we used statistical nonparametric mapping (SnPM).[48] The use of SnPM in eLORETA has been validated[49,50] and utilized in previous clinical studies.[41,51] Differences in cortical oscillations between groups in each frequency band were assessed by voxel-by-voxel independent sample *F*-ratio-tests with a frequency wise normalization. To correct for multiple comparisons across all voxels and all frequencies, a total of 5000 permutations were used to calculate the critical probability threshold (5% probability level).

Next, CSD values were extracted at those ROI that differed between groups and their association with LPS-3 and 2-back tasks performance scores was assessed by linear regression models using neuropsychological performance scores as dependent variables and CSD values, diagnostic group, age, and years of education as independent variables. To test whether the associations between CSD values and neuropsychological performance differed between groups, an interaction term between group and CSD values was included. In addition to this ROI approach, a whole brain analysis was performed by correlating voxel-wise these performance measures with CSD. Furthermore, to correct for multiple testing, this whole brain analysis was based on 5000 permutations to

determine the empirical probability distribution for the maximal statistics under the null hypothesis.[41,52]

To assess group differences in lagged phase synchronization, we fitted a linear mixed-effects model using lagged phase synchronization of the ROI pairs (171 pairs) as the dependent variable and Euclidian distance (within-subjects) and group (between-subjects) along with their interaction as independent variables. The model also included an intercept term that randomly varied per individual. To investigate the impact of positive and negative symptoms on the lagged phase synchronization as a function of anatomical distances, we applied linear mixed-effects models that additionally included BPRS positive and negative symptoms as independent variables. Furthermore, these analyses were repeated for each of the seven different frequencies and corrected for multiple comparison using the Benjamini–Hochberg method.[53]

Results

Sample Description

Until August 2013, 134 ARMS patients and 97 HC were recruited for the ***FePsy*** study. Of these, 63 ARMS and 29 HC had sufficient EEG and follow-up data to be included in the present study. Twenty-three of the included ARMS patients had made a transition to psychosis (ARMS-T) during the follow up and 40 had not (ARMS-NT). None of those who made a transition converted to psychotic mood disorder. The 71 ARMS individuals that were excluded from this study did not differ from the included ARMS individuals with regard to gender, sex, years of education, and BPRS total and positive symptoms scores. Demographic and clinical characteristics of the 3 groups (ie, HC, ARMS-T, and ARMS-NT) are shown in table 1. There was a small overall difference in age (P = .046), which was due to a lower age in HC compared to ARMS-NT, significant at a trend level (P = .053). Furthermore, ARMS-T patients had higher positive symptoms than ARMS-NT (P = .005). Almost all ARMS individuals were antipsychotic naïve; only 4 ARMS individuals (4/63) had received low doses of second-generation antipsychotic medication during no more than 3 weeks for behavioral control by the referring psychiatrist or general practitioner prior to study inclusion.

Table 1. Demographic and Clinical Characteristics of HC, ARMS-T, and ARMS-NT Individuals

	HC N = 29	ARMS-NT N = 40	ARMS-T N = 23	P Value
Gender				.597
Women	14 (48.3%)	15 (37.5%)	11 (47.8%)	
Men	15 (51.7%)	25 (62.5%)	12 (52.2%)	
Age	22.4 (5.02)	26.5 (8.42)	26.3 (7.13)	.046
Years of education	11.9 (1.93)	11.6 (3.49)	11.2 (2.41)	.693
Antidepressants currently				1.000
No		30 (75.0%)	17 (73.9%)	
Yes		10 (25.0%)	6 (26.1%)	
Antipsychotics currently				.619
No		38 (95.0%)	21 (91.3%)	
Yes		2 (5.00%)	2 (8.70%)	
Mood stabilizer currently				.365
No		40 (100%)	22 (95.7%)	
Yes		0 (0.00%)	1 (4.35%)	
Tranquilizer currently				.713
No		35 (87.5%)	19 (82.6%)	
Yes		5 (12.5%)	4 (17.4%)	
BPRS positive symptoms		6.33 (2.39)	8.67 (2.71)	.001
BPRS negative symptoms		5.60 (2.72)	5.40 (2.74)	.795
BPRS total score		37.7 (10.5)	42.1 (9.89)	.137
Risk group				.116
Prepsychotic only (APS or BLIPS)		25 (62.5%)	18 (78.3%)	
Genetic risk only		3 (7.50%)	0 (0.00%)	
Mixed prepsychotic + genetic		6 (15.0%)	5 (21.7%)	
Unspecific only		6 (15.0%)	0 (0.00%)	
LPS (nonverbal IQ)	119 (9.31)	115 (10.6)	112 (14.3)	.204
2-back task correct responses	13.5 (1.46)	12.0 (3.24)	11.2 (2.51)	.044
Days between EEG and transition to psychosis			423 (449)	

Note: HC, healthy controls; ARMS-NT, at-risk mental state patients without later transition to psychosis; ARMS-T, at-risk mental state patients with later transition to psychosis; BPRS, Brief Psychiatric Rating Scale; LPS, Leistungsprüfsystem; APS, attenuated psychotic symptoms; BLIPS, brief, limited intermittent psychotic symptoms. Categorical and continuous variables were compared by Pearson χ^2 (or Fisher's exact tests if any expected cell frequencies were <5) and ANOVAs, respectively.

Source Localization

The average CSD in ARMS-T, ARMS-NT, and HC at each frequency band are depicted in figure 1. In ARMS-T and ARMS-NT, the highest CSD values were present in the delta (0.82 vs 0.63 μA/mm^2) followed by the gamma frequency band (0.67 vs 0.57 μA/mm^2), whereas in HC they were in alpha2 (0.55 μA/mm^2) and delta (0.43 μA/mm^2), respectively. In ARMS-T patients delta activity seemed to be relatively distributed throughout the cortex, particularly in frontal and parieto-occipital areas, while in HC and ARMS-NT delta activity was more localized in the frontal cortex. In the gamma band, source frontal activity seemed to progressively increase from HC to ARMS-NT to ARMS-T. Interestingly, statistical analyses confirmed that ARMS-T had increased gamma activity in the medial prefrontal cortex (mPFC) bilaterally (BA 10), with a global maximum in the left hemisphere ($X = -5$, $Y = 66$, $Z = 15$, $t = 4.59$, $P < .05$, corrected) (see figure 2a).

Current Source Analyses and Neurocognitive Measurements

A linear regression model with cognitive performance in the LPS-3 as dependent variables and CSD activity in the gamma frequency band at the mPFC and group (ARMS-T vs HC) as independent variables revealed a significant main effect of group ($P < .001$, corrected) and interaction between group and mPFC activity ($P < .001$, corrected). This interaction was due to a positive relationship between LPS-3 and mPFC activity in the ARMS-T group ($P < .001$, corrected) but not in HC ($P = .140$, corrected) (see figure 2b). In a similar model including performance in the 2-back task as dependent variable, there were no significant main effect of mPFC activity and interaction effect between mPFC activity and group when corrected for multiple comparisons. These results were also found using conventional EEG measurements (supplementary appendix 1). A whole brain voxel-wise correlation analysis revealed that the CSD of gamma oscillations was highly correlated with LPS-3 performance in ARMS-T ($r = .734$, $P < .001$, corrected), but not in ARMS-NT and HC, and the global maximum was located at ($X = -5$, $Y = 65$, $Z = 15$) (supplementary appendix 2).

Lagged Phase Synchronization Across Distributed Brain Regions

Linear mixed-effects models with lagged phase synchronization as dependent variables, Euclidian distance, group and their interaction as independent variable and a random intercept per subject, revealed significant main effects of Euclidian distance for each frequency band (all Ps $< .001$, corrected). This was due to decreased lagged phase synchronization with increasing distances between the ROIs (171 pairs) in all frequencies except for the delta band, which demonstrated an opposite association. In addition, there was a significant interaction between group and Euclidian distance for lagged phase synchronization

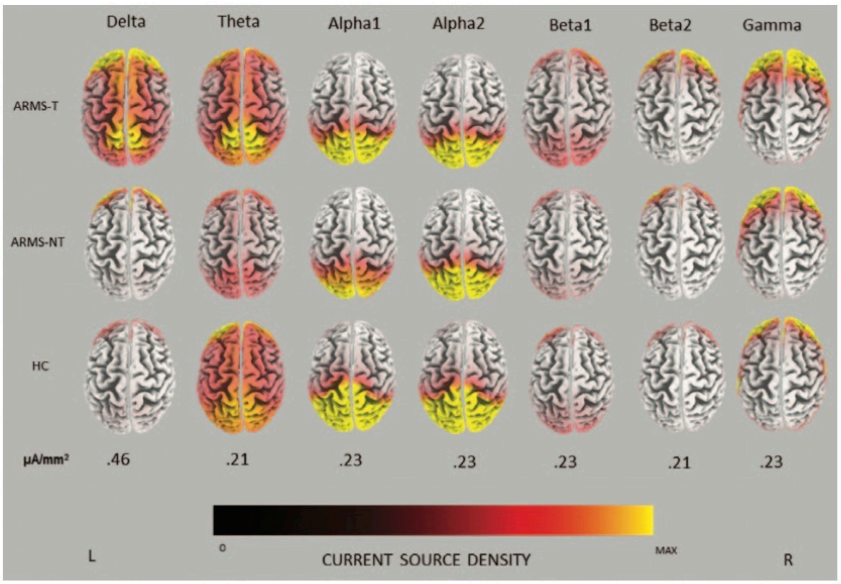

Fig. 1. For illustrative purposes, the average current source density (μA/mm^2) by group and frequency bands.

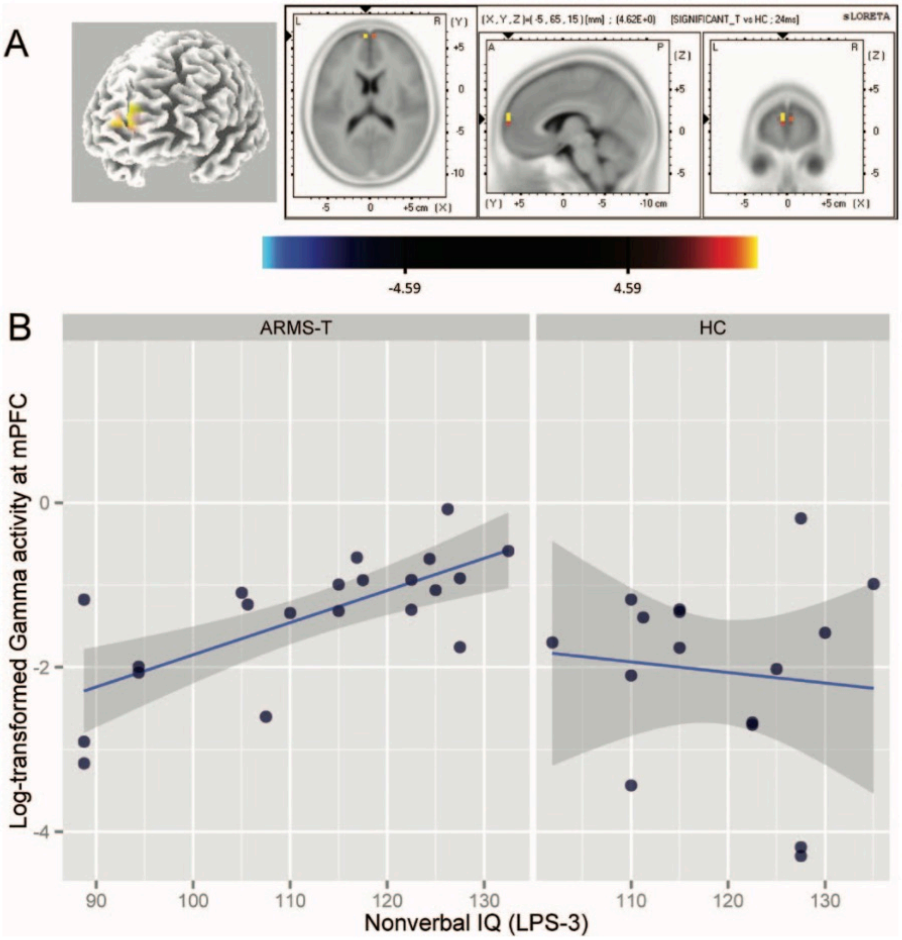

Fig. 2. (A) eLORETA statistical map of gamma band differences between ARMS-T and HC and (B) correlations between gamma activity (μA/mm²) at the medial prefrontal cortex (mPFC) and LPS-3 performance in ARMS-T and HC.

of beta1 oscillations ($P < .001$, corrected), which was due to a stronger decrease of lagged phase synchronization with increasing anatomical distance in the ARMS-T group compared to the ARMS-NT and HC groups (see figure 3).

Moreover, a linear mixed-effect model that additionally included BPRS positive symptoms as an independent variable revealed a significant second order interaction between lagged phase synchronization, distance and BPRS positive symptoms in the beta1 frequency band ($P = .002$, corrected), indicating that higher positive symptoms in the ARMS-T group was associated with a particular strong decrease of lagged phase synchronization with increasing distance (see figure 4a). The same interaction occurred with negative symptoms ($P = .022$, corrected) (see figure 4b). In both models, the interaction between Euclidian distance and group remained significant, indicating that this interaction was not due to different psychopathology in ARMS-T and ARMS-NT.

Discussion

In this study, we assessed by means of electrophysiological neuroimaging methods the CSD distribution and lagged-phase synchronization of neural oscillations across brain areas in patients at-risk for psychosis and HC. Consistent with our predictions, we found: (1) in comparison to HC, increased CSD of frontal gamma oscillations (30–50 Hz) in those patients who later transitioned to psychosis. Moreover, in ARMS-T gamma activity was positively

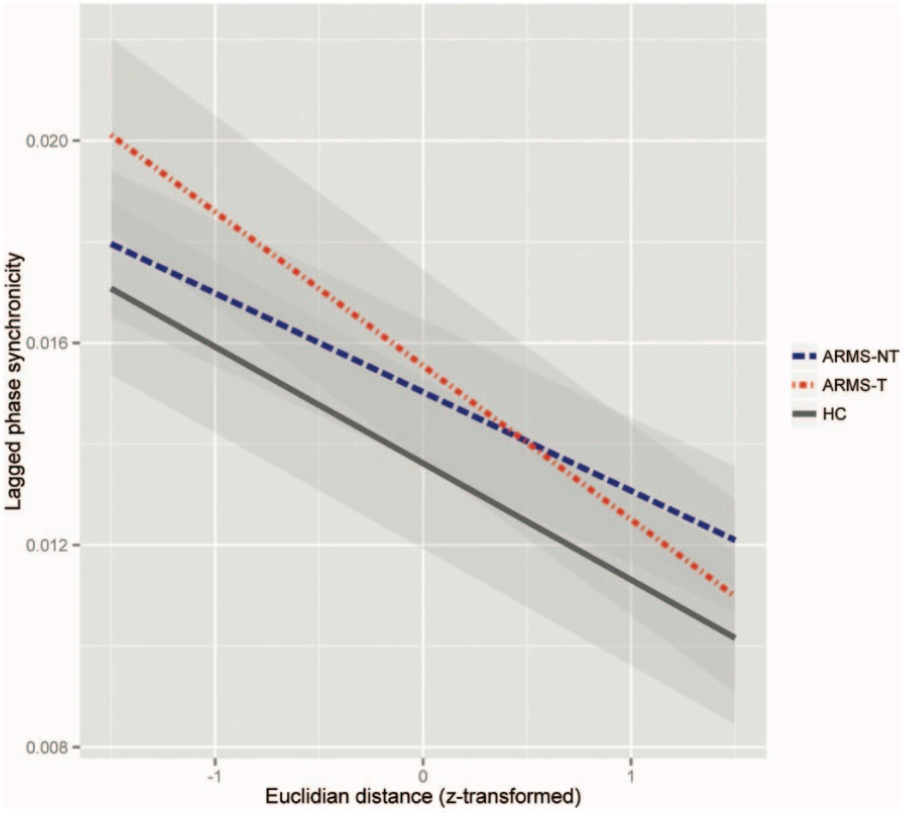

Fig. 3. The lagged phase-synchronization of the beta 1 frequency band as a function of distance. Shaded areas cover regression coefficients with ±1 SE.

correlated with cognitive performance as assessed by the LPS-3. (2) We revealed that the inverse relationship between lagged phase synchronization and Euclidian distance was steeper in the ARMS-T patients than the other groups. This effect was most pronounced in patients with elevated negative and positive symptoms. These findings provide strong evidence that patients who will later make the transition to psychosis are characterized by impairments in neural oscillations.

CSD Analyses

The revealed alteration in mPFC gamma oscillations in ARMS-T patients is in line with numerous studies reporting abnormal gamma oscillations in schizophrenia[2,54,55] and extends these findings by demonstrating that prefrontal gamma oscillations are already affected in high-risk patients that later transitioned to psychosis. Although both an increase and a decrease of gamma oscillations have extensively been documented in patients suffering from psychosis, an increase has mostly been found in unmedicated patients exhibiting positive symptoms.[11] This is in line with our ARMS-T patients who fit these criteria and could explain the here revealed increase in the medial prefrontal gamma oscillations.

As the mPFC has been shown to be modulated by gamma oscillations[56] and to be associated with seemingly disparate cognitive functions such as detecting high-order relationships,[57–60] planning and visualizing the future[61] and constructing social and emotional judgments,[62] our finding of increased gamma activity suggests that ARMS-T patients, already at baseline, have an impaired mPFC that could potentially explain cognitive abnormalities.[63,64] Indeed, we found that gamma oscillation in mPFC [Brodmann area (BA) 10] correlated with neurocognitive performance in the LPS-3, a task in which patients are asked to find which item does not belong to a series of shapes. Such a detection of a higher-order relationship between individual entities was previously found to be associated with activation in BA 10 in semantic[57,59]

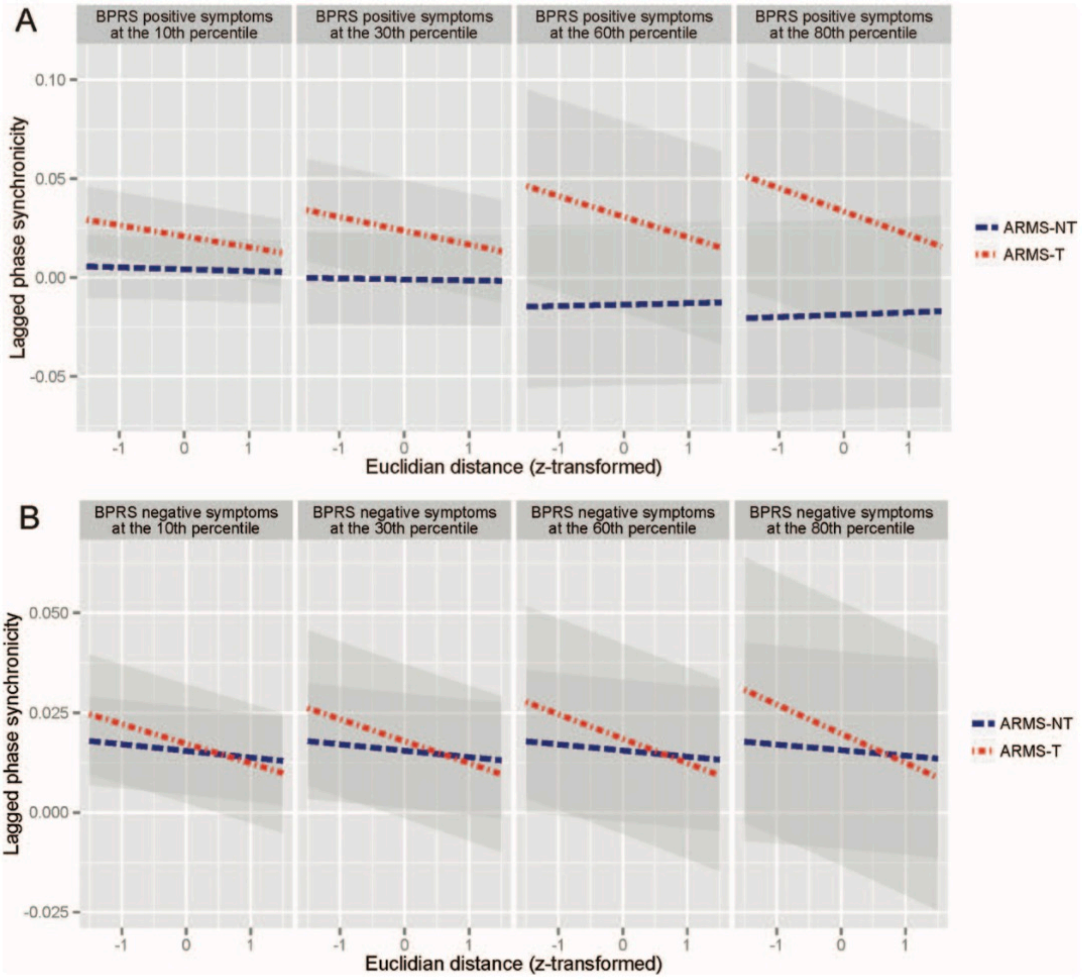

Fig. 4. (A) The lagged phase-synchronization of the beta 1 frequency band as a function of distance for each of 4 different values of BPRS positive symptoms. (B) The lagged phase-synchronization of the beta 1 frequency band as a function of distance for each of 4 different values of BPRS negative symptoms. Shaded areas cover regression coefficients with ±1 SE.

and visual-based tasks,[58,60] which is in line with the here revealed association between LPS-3 performance and mPFC gamma oscillations. However, the correlation between LPS-3 performance and gamma oscillations was positive, suggesting that increased medial prefrontal gamma oscillations in the ARMS-T group may be an adaptive and compensatory process. A speculative explanation would be that patients with a high capacity to detect higher-order relationships, as indexed by the LPS-3 test and by gamma oscillation in the BA10, are more cognitively equipped to make sense of their altered psychological state.

Lagged Phase Synchronization Across Distributed Brain Regions

We revealed that ARMS-T patients show stronger decreasing lagged phase synchronicity with increasing Euclidian distance than ARMS-NT and HC (figure 3). This negative association is particularly present in patients with high positive symptoms (figure 4).

Thus, through the increased synchronization in the shorter inter-regional distances of the brain characterized in ARMS-T individuals, the influence of the long-range synchronicity is reduced. This could result from the disruption in the volume and organization of anatomical

connections, which is supported by the findings of reduced grey matter volume in ARMS-T[65] and its association with beta oscillations.[3] Therefore, this could lead to the situation that distributed cortical areas can no longer communicate efficiently and that psychological entities like perception and cognition are no longer adequately integrated. These findings support the increasingly accepted notion that the neuropsychological impairments associated with schizophrenic psychoses are due to distributed impairments involving the coordinated activity among numerous cortical areas.[3] Importantly, given that we observed increased synchronization in the beta1 band already before transition to psychosis, this could indicate an increased liability for psychosis and thereby help to improve the prediction of psychosis.

Limitations

The results of the present study are constrained by a number of limitations: All data were acquired using a relatively low-density EEG system which is commonly used in the clinical field for practical reasons. Even though numerous recent studies have shown that CSD and connectivity analyses during resting-state could reliably be performed using a 19 channels EEG system,[66–68] we believe that the true potential of the eLORETA analyses could not be fully utilized. Moreover, to control for the strong correlation between adjacent voxels in the phase synchronization analyses, we could only choose 19 ROIs that would be measured by 19 channels and yield only 171 connections. Therefore, future studies should conduct these analyses again using higher density EEG systems.

Conclusion

Taken together, our result of a heightened gamma activity in the mPFC in ARMS-T patients could potentially reveal the neural underpinnings for an abnormal cognitive integration. Moreover, the increased lagged phase synchronicity characterized across smaller inter-regional brain areas in the beta1 frequency suggests anatomical abnormalities that could be hindering the proper communication between various cortical areas. These findings provide strong evidence that patients who will later make the transition to psychosis are characterized by impairments in neural oscillations.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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Publication 2: “Prediction of psychosis using neural oscillations and machine learning in neuroleptic-naïve at-risk patients“

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ORIGINAL INVESTIGATION

Prediction of psychosis using neural oscillations and machine learning in neuroleptic-naïve at-risk patients

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ABSTRACT

Objectives: This study investigates whether abnormal neural oscillations, which have been shown to precede the onset of frank psychosis, could be used towards the individualised prediction of psychosis in clinical high-risk patients. *Methods*: We assessed the individualised prediction of psychosis by detecting specific patterns of beta and gamma oscillations using machine-learning algorithms. Prediction models were trained and tested on 53 neuroleptic-naïve patients with a clinical high-risk for psychosis. Of these, 18 later transitioned to psychosis. All patients were followed up for at least 3 years. For an honest estimation of the generalisation capacity, the predictive performance of the models was assessed in unseen test cases using repeated nested cross-validation. *Results*: Transition to psychosis could be predicted from current-source density (CSD; area under the curve [AUC] = 0.77), but not from lagged phase synchronicity data (LPS; AUC = 0.56). Combining both modalities did not improve the predictive accuracy (AUC = 0.78). The left superior temporal gyrus, the left inferior parietal lobule and the precuneus most strongly contributed to the prediction of psychosis. *Conclusions*: Our results suggest that CSD measurements extracted from clinical resting state EEG can help to improve the prediction of psychosis on a single-subject level.

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Introduction

Schizophrenic psychoses are increasingly acknowledged as neurodevelopmental disorders whose signs and symptoms can sometimes be observed as early as in childhood (Insel 2010). A delay between the diagnosis and the treatment of these disorders ranges from 1 to 3 years (Riecher-Rössler et al. 2006) and could result in severe negative ramifications such as a worse functional outcome (Insel 2010), loss of grey-matter volume (Fusar-Poli et al. 2011a), higher cognitive deterioration (Amminger et al. 2002), higher dosage of neuroleptics needed (McGorry et al. 1996) and higher overall treatment costs (Moscarelli 1994). By contrast, therapeutic actions in the earliest phases of the disease could considerably improve the prognosis of these individuals (Stafford et al. 2013).

In the last two decades, there has been increased interest in the early detection of psychosis and reliable criteria have been established internationally to detect an at-risk mental state (ARMS) for psychosis. As only about one-third of ARMS patients eventually develop psychosis (Fusar-Poli et al. 2012), and about one-third remit from their risk state (Simon et al. 2013), further risk-stratification is required to identify subgroups with specific needs and response patterns that could improve the cost–benefit ratio of preventive interventions (Ruhrmann et al. 2014). Although individualised prediction models for psychosis based on structural magnetic resonance imaging (MRI) achieved promising predictive accuracies (Koutsouleris et al. 2014), it has not been investigated whether the same could be obtained using more cost-efficient measures, such as clinical resting-state EEG.

Although both an increase and decrease in gamma activity has been noted in patients with schizophrenia (Herrmann and Demiralp 2005), heightened activity has consistently been reported in unmedicated patients suffering from positive symptoms while the opposite has largely been found in those suffering from negative symptoms (Herrmann and Demiralp 2005; Lee et al.

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2003). While the gamma band tends to be associated with the precise timing of neural interactions in localised small networks (Uhlhaas and Singer 2013), the beta band is known to be predominantly involved in modulating neural communications, albeit with a reduced precision, amongst broadly distributed cortical networks (Kopell et al. 2000). For instance, it has been shown that beta oscillations mediate interactions of distributed functional networks involved in multimodal sensory processing and sensory-motor coordination during normal brain functioning (Uhlhaas and Singer 2013). Interestingly, all these attentional processes are deeply perturbed in patients with schizophrenia (Morris et al. 2012), suggesting a disturbed long-ranged neural communication.

Given these accumulated evidence on the associations between abnormal high-frequency oscillations and schizophrenic psychoses, high-frequency oscillations may also be altered in ARMS patients with later transition to full blown psychosis (ARMS-T) and could therefore serve as neurophysiological biomarkers for predicting psychosis. In fact, in a recent study Ramyead et al. (2014) have demonstrated, using a univariate approach, that ARMS-T patients are characterised by atypical gamma current-source density (CSD) in the medial prefrontal cortex along with abnormal lagged phase synchronisation (LPS) of beta1 oscillations across brain areas. However, they did not investigate whether these group differences could be exploited to make accurate predictions on a single-subject level, thereby potentially contributing to informed clinical decision-making. Thus, the aim of this study was to investigate whether an accurate prediction of psychosis can be achieved by CSD, LPS or both measures at the same time in order to detect potential signatures associated with later transition to psychosis. To this end, we applied state-of-the-art machine-learning algorithms to source localised clinical EEG measures.

In the past few years, there has been an increased interest in applying multivariate pattern-recognition algorithms in various fields, ranging from genomics (Liu et al. 2013) to cybersecurity (Dua and Du 2011), with substantial success. Although these techniques have been successfully applied to neuroanatomical (Koutsouleris et al. 2014) and neuropsychological data (Koutsouleris et al. 2012) in order to predict psychosis in ARMS patients, no study has applied them to clinical resting-state EEG data. This is surprising as in many early detection centres for psychosis, resting-state EEG is routinely used in ARMS patients for signs of organic brain disorders such as limbic encephalitis or epilepsy with relatively low cost. Moreover, neuronal oscillations have been strongly associated with the pathophysiology of schizophrenic psychoses (Uhlhaas and Singer 2013). Furthermore, previous studies using clinical EEG for prediction of psychosis are limited as they included at-risk patients already medicated with antipsychotics (up to about 40% in one instance (van Tricht et al. 2014)). These medications have been shown to change neural oscillations (Centorrino et al. 2002) and are likely to alter the natural trajectory of psychosis, therefore potentially yielding misleading biomarkers.

To overcome these weaknesses, we set out to employ a machine-learning algorithm, the least absolute shrinkage and selection operator (LASSO), that detects multivariate patterns of high-frequency oscillations across different brain regions on the same sample of patients as in our previous study (Ramyead et al. 2014). However, compared to the previous sample, we excluded the patients who were already medicated with neuroleptics due to the reasons mentioned earlier. To make use of three-dimensional CSD and LPS of high-frequencies (beta1, beta2, gamma) oscillations as input variables, we applied the inverse solution technique exact low-resolution electromagnetic tomography (eLORETA), which allows for a reliable source localisation of brain activity analyses at individual frequencies (Pascual-Marqui et al. 2011). Finally, we conducted our analysis on a group of ARMS patients which were followed-up over the course of at least three years to determine whether they later made transition to psychosis (ARMS-T) or not (ARMS-NT). We hypothesised that – based on their specific pattern of CSD and/or LPS in the high frequencies at 19 cortical regions of interests (ROIs) – ARMS-T individuals could be separated from ARMS-NT individuals with good accuracy.

Methods

Setting and recruitment

The EEG data analysed in this study were collected as part of the Basel ***F***rüh***e***rkennung von ***Psy***chosen (***FePsy***) project, a prospective multilevel study aiming to improve the early detection of psychosis (Riecher-Rössler et al. 2007; Riecher-Rössler et al. 2009). The study was approved by the ethics committee of the University of Basel. All participants provided written informed consent. Patients recruited for this study were help-seeking consecutive referrals to the *FePsy* Clinic at the University Psychiatric Clinics Basel, which was specifically set up to identify, assess, and treat individuals in the early stages of psychosis. Most participants were referred to the early detection clinic via the University Psychiatric Outpatient Department of Basel or a psychiatrist in private practice. Some individuals

were also referred from other physicians, including general practitioners, or came on their own.

Screening procedure

The Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al. 2008) was applied to identify ARMS individuals. The BSIP is largely based on the PACE inclusion/exclusion criteria (Yung et al. 1998) and has been shown to have a high predictive validity and a good interrater reliability (Riecher-Rössler et al. 2008). Exclusion criteria for patients were age <18 years, insufficient knowledge of German, IQ < 70, previous episode of schizophrenic psychosis treated with antipsychotics, psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed depression or borderline personality disorder. For this study, we included all ARMS patients that were recruited for the *FePsy* study between March 2000 and August 2012 and had a clinical EEG session of at least 15 min at baseline assessment. They were followed-up at regular intervals in order to distinguish those who later transitioned to frank psychosis (ARMS-T) from those who did not (ARMS-NT). During the first year of the follow-up, ARMS individuals were assessed for transition to psychosis monthly, during the second and third years they were assessed every 3 months, and thereafter annually using the transition criteria of Yung et al. (1998). In this study, individuals were only classified as ARMS-NT if they had a follow-up duration of at least 3 years and did not develop frank psychosis.

Assessment of positive and negative psychotic symptoms

The Brief Psychiatric Rating Scale Expanded (BPRS-E; Lukoff et al. 1986; Ventura et al. 1993) was used to assess positive and negative psychotic symptoms. The positive psychotic symptom scale was based on the four items hallucinations, suspiciousness, unusual thought content, and conceptual disorganisation and the negative psychotic symptom scale was based on the items blunted affect, psychomotor retardation and emotional withdrawal, as defined by Velligan et al. (2005).

EEG recordings

EEG data were recorded at the University Hospital of Basel. Patients sat in a quiet room in an eyes-closed resting-state condition for about 20 min. Every 3 min, subjects were asked to open their eyes for a period of 5–6 s. At any signs of behavioural and/or EEG drowsiness, the patients were verbally asked to open their eyes. EEG data were sampled at a rate of 250 Hz by 19 gold cup electrodes (Nicolet Biomedical Inc., Madison, Wisconsin) referenced to linked ears. Electrodes impedances were kept below 5Ω.

Artefact rejection

EEG pre-processing was performed using Brain Vision Analyzer© 2.0 software (Brain Products GmbH, Munich, Germany). We processed each EEG in parallel split into two branches, one filtered at 0.5 Hz and one at 1 Hz. We did so in order to apply the Independent Component Analysis (ICA) matrix from the most stable signal (1 Hz) to the one that conserved the most signal (0.5 Hz). Both branches were handled in the same way up to the step that involved re-referencing to the common average. As a first step, artefact rejection was performed manually, based on visual inspection, to remove epochs containing extreme ocular artefacts, muscles and/or cardiac contamination and bad signals due to random movements. Biased extended Infomax ICA analyses were then performed for the removal of residual eye movements, eye-blinking, muscles and non-biological components contaminated with high gamma frequencies of 50 Hz and above as measured by Fast Fourier Transform (FFT) of the ICA components (resolution at 1 Hz, power μV2, Hanning window length of 10%). After applying the ICA corrected matrix of the data filtered at 1 Hz to the one filtered at 0.5 Hz, we re-referenced the data to common average. Finally, another manual rejection based on visual inspection was performed to exclude remaining artefacts as mentioned earlier.

CSD analyses

EEGs were transformed into reference-free CSD estimates achieved by the Laplacian Weighted Minimum Norm algorithm (Pascual-Marqui 2007). Compared to conventional EEGs based on voltage, accumulated evidence have indicated that the use of CSD as a measure of brain activity allows reliable spatial analysis (Michel et al. 2004) by disentangling the EEG signals from various biological and non-biological artefacts, thus yielding measures that more closely represent the neuronal current generators (Tenke et al. 2011).

The electrode montage in the present study has been shown to be an acceptable EEG spatial sampling for the estimation of cortical sources of eyes-closed resting-state EEG rhythms as these oscillatory rhythms are widely characterised across all human cerebral cortex when compared to the demarcated functional topography of event-related EEG changes. Consequently, the oscillatory rhythms acquired during eye-closed

resting-state EEG can properly be sampled with a relatively low number of electrodes, as opposed to the higher density electrode montage required for observing the functional topography of stimuli-related EEG activity (Babiloni et al. 2013). This relatively low-spatial sampling of EEG oscillatory rhythms is robust as LORETA solutions are intrinsically maximally smoothed at source space thanks to its regularisation procedure (Pascual-Marqui et al. 1994; Babiloni et al. 2013;).

To compute the intracortical CSD of neural oscillations, we used eLORETA (Pascual-Marqui et al. 2011) on EEG data segmented into 2-s epochs (671 epochs on average, and groups did not significantly differ in the number of segments). eLORETA is a neurophysiological imaging technique based on weighted minimum norm inverse solution procedures allowing for the 3D modelling of the EEG CSD with an exact localisation performance, with a high correlation of neural sources that are in close proximity. Numerous studies based on neuroimaging tools, such as functional (Mulert et al. 2004) and structural MRI (Worrell et al. 2000), positron emission tomography (PET; Zumsteg et al. 2005) and intracranial EEG recordings (Zumsteg et al. 2006) have validated LORETA as an efficient and reliable tool to study brain activity. Compared to the first version of LORETA (Pascual-Marqui et al. 1994), the most recent version, namely, eLORETA has no localisation bias in the presence of structured noise (Pascual-Marqui 2007).

In eLORETA, a three-shell spherical head model (brain, scalp and skull compartments) is assumed and the solution space is restricted to the cortical grey-matter and the hippocampus. In total, the solution space comprises 6239 voxels of $5 \times 5 \times 5$ mm each. The head model for computing the lead field is based on the Montreal Neurological Institute (MNI) brain MRI average (Pascual-Marqui et al. 1994). The CSD were calculated for the high frequency bands: beta1 (13–21 Hz), beta2 (21–30 Hz) and gamma (30–50 Hz).

LPS analyses

For spatially unbiased LPS analysis we defined ROIs based on the MNI coordinates of the cortical voxel underlying the 19 electrode sites (ROIs coordinates are given in Supplemental Table S1, available online). We used a single voxel for each ROI because eLORETA's spatial resolution is relatively low, and expanding the ROI to neighbouring voxels could potentially bias the analysis due to the high correlation among them (Canuet et al. 2012). Next, we computed the LPS between all 19 ROIs resulting in a relatively high number (i.e., 171) of pairwise combinations. LPS quantifies the non-linear relationship between 2 ROIs after the instantaneous zero-lag contribution has been removed. Removing this instantaneous zero-lag contribution has been shown to eliminate non-physiological artefacts, such as volume conduction, which biases relationship measurements such as instantaneous connectivity. The Euclidian distance between ROI1 ($x1$, $y1$, $z1$) and ROI2 ($x2$, $y2$, $z2$) were calculated using the Pythagorean theorem: $\sqrt{[(x2-x1)2+(y2-y1)2+(z2-z1)2]}$ and were subsequently standardised into z-scores.

LPS computes the corrected phase synchrony value between signals in the frequency domain based on normalised Fourier transforms. It is therefore a measure of nonlinear functional connectivity. To reduce volume conduction and related artefacts, the instantaneous zero-lag contribution has been excluded from the total phase synchronisation yielding only lagged synchronisation. The classical total "squared" phase synchronisation, which is highly contaminated by the instantaneous artifactual component, is defined as:

$$\begin{aligned}\varphi^2_{x,y}(\omega) &= \left|f_{x,y}(\omega)\right|^2 \\ &= \left\{\mathrm{Re}\left[f_{x,y}(\omega)\right]\right\}^2+\left\{\mathrm{Im}\left[f_{x,y}(\omega)\right]\right\}^2\end{aligned} \quad (1)$$

with:

$$f_{x,y}(\omega) = \frac{1}{N_R}\sum_{k=1}^{N_R}\left[\frac{x_k(\omega)}{|x_k(\omega)|}\right]\left[\frac{y_k^*(\omega)}{|y_k(\omega)|}\right] \quad (2)$$

Where $x_k(\omega)$ and $y_k(\omega)$ correspond to the discrete Fourier transforms of the two signals of interest x and y at frequency ω for the kth EEG, Re[C] and Im[C] denote the real and imaginary parts of a complex number C; the latter explains the cycle of C; and the superscript "*", denotes a complex conjugate. The instantaneous (zero-lag) connectivity component is closely related to the real part of the phase synchronisation. LPS, which statistically partials out the instantaneous component of the total connectivity, is defined as:

$$\varphi^2_{x,y}(\omega) = \frac{\left\{\mathrm{Im}\left[f_{x,y}(\omega)\right]\right\}^2}{1-\left\{\mathrm{Re}\left[f_{x,y}(\omega)\right]\right\}^2} \quad (3)$$

In order to calculate the slope between LPS and distances, a linear model was created for all the 171 pairs, which included LPS values as dependent variable and the distance between each of the 19 ROIs as independent variable. Therefore, for each individual, three LPS values (beta1, beta2 and gamma) were extracted. These values correspond to the slope of the linear model which summarises the relationship between LPS at increasing distances between the 19 ROIs. These LPS values were then standardised before feeding them into the LASSO.

Defining the ROIs

For all analyses, we defined ROIs based on the MNI coordinates of the cortical voxel at 19 sites (Canuet et al. 2012) (Supplemental Table 1 available online). For each ROI, we calculated activity at the centroid voxel. We did so as expanding to neighbouring voxels could potentially bias the analysis due to the potential correlation amongst them.

Prediction of transition to psychosis

All multivariate classification analyses were conducted using the R statistical environment (R Core Team 2014). As classification algorithm, we used the L1 regularised version of the logistic regression model, that is, the so called LASSO, as implemented in the R add-on package liblineaR (Helleputte 2013). We chose the LASSO because it performs variable selection and regression coefficient estimation simultaneously and thereby gives rise to models that are sparse and easy to interpret and at the same time still have very good predictive performance. The LASSO selects the most important variables by shrinking the regression coefficient of unimportant variables to zero. It has been demonstrated that the LASSO is more stable and accurate than traditional variable selection methods, such as backward elimination and best subset selection (Tibshirani 1996). Thus, it is highly suitable for high-dimensional data problems (i.e., small event per variable ratio). Another advantage of the LASSO model is that it can easily be summarised by a regression function, whereas most other machine-learning methods, such as for instance support vector machines, lack an intuitive understanding and thus are much more difficult to communicate and validate.

To avoid optimistically biased estimates of performance and to protect against overfitting, we strictly separated the processes of training and testing the classifier. Specifically, we applied nested cross-validation with 10 folds and10 repetitions both in the inner and the outer loop using the R add-on package MLR (Bischl et al. 2015). The inner loop was used to search for the optimal tuning parameter lambda, whereas the outer loop was used to evaluate the predictive performance of the model. For tuning the model, we performed a grid search over a sequence of the 10 different values of lambda between 0.5 and 15. That is, for each value of lambda the cross-validated balanced accuracy (BAC) was estimated using 10-fold cross validation with 10 repetitions and the lambda value with the highest performance was picked. Since this was repeated at each iteration of the outer loop, the number of times a LASSO model was fitted amounted to $10 \times 10 \times 10 \times 10 \times 10 = 100{,}000$. To mitigate problems of class imbalance, we gave more weight to the ARMS-T class than to the ARMS-NT class during model fitting. Specifically, ARMS-T observations were given weights of 1.94, which is the number of ARMS-NT divided by the number of ARMS-T, and ARMS-NT observations were given weights of 1.

To investigate the contribution of each EEG modality (i.e., CSD and LPS), we trained and tested three different classifiers. The first was based on the 57 CSD measures (three frequencies at 19 ROIs), the second was based on the three LPS measures, and the third was based on CSD and LPS measures combined. For the latter, we applied a meta-learner that learned from the predictions of the CSD and LPS based learners. As classification algorithm for the meta-learner, the same method was applied as for the base learners (i.e., LASSO tuned with grid search and 10-fold cross-validation with 10 repetitions).

We restricted potential predictors to those frequencies consistently found to be altered in the resting-state psychosis literature. This procedure is in accordance with text books on clinical prediction modelling (Steyerberg 2009) which recommend to select candidate predictor variables based on the literature, especially in small samples.

Results

Sample description

From March 2000 to August 2012 a total of 134 ARMS patients were recruited into the *FePsy* study. Of these, 53 ARMS had at least 15 min of EEG data, were antipsychotic-naïve and had sufficient follow-up data to be included in the present study. Eighteen of the included ARMS patients made a transition to psychosis (ARMS-T) during the follow-up and 35 did not (ARMS-NT). None of those who made a transition converted to affective psychosis. The 60 ARMS individuals that were excluded from this study did not differ from the included ARMS individuals with regard to age, gender, sex, years of education, and BPRS total and positive symptoms scores. The clinical characteristics and demographics of the ARMS-T and ARMS-NT groups are shown in Table I. The only overall difference in ARMS-T patients was a slightly higher positive symptoms score ($P = 0.035$).

Prediction of transition to psychosis

The predictive performances in unseen test cases of the classifiers based on CSD, LPS, and both combined (stacked learner) are summarised in Table II and their

Table I. Demographic and clinical characteristics at EEG assessment.

	ARMS-NT ($N = 35$)	ARMS-T ($N = 18$)	P value
Gender			0.672
Women	12 (34.3%)	8 (44.4%)	
Men	23 (65.7%)	10 (55.6%)	
Age	25.8 (7.36)	26.7 (7.64)	0.687
Years of education	11.3 (3.24)	11.0 (2.27)	0.684
Antidepressants currently			1.000
No	26 (74.3%)	14 (77.8%)	
Yes	9 (25.7%)	4 (22.2%)	
Antipsychotics currently: no	35 (100%)	18 (100%)	
Mood stabiliser currently			0.340
No	35 (100%)	17 (94.4%)	
Yes	0 (0.00%)	1 (5.56%)	
Tranquilizer currently			0.469
No	30 (85.7%)	14 (77.8%)	
Yes	5 (14.3%)	4 (22.2%)	
Substance use disorders			1.000
No	29 (87.9%)	13 (86.7%)	
Yes	4 (12.1%)	2 (13.3%)	
Mood disorder:			0.099
No	25 (75.8%)	7 (46.7%)	
Yes	8 (24.2%)	8 (53.3%)	
Anxiety disorders			1.000
No	27 (81.8%)	13 (86.7%)	
Yes	6 (18.2%)	2 (13.3%)	
BPRS Positive symptoms	6.39 (2.33)	7.83 (2.18)	0.035
BPRS Negative symptoms	5.65 (2.52)	5.41 (2.90)	0.782
BPRS total score	37.9 (11.0)	40.2 (9.86)	0.462

ARMS-NT, at-risk mental state patients without later transition to psychosis; ARMS-T, at-risk mental state patients with later transition to psychosis; BPRS, Brief Psychiatric Rating Scale. Categorical and continuous variables were compared by Pearson's $\chi 2$ (or Fisher's exact tests if any expected cell frequencies were <5) and ANOVAs, respectively. Numbers in brackets indicate mean and SD for continuous variables and absolute numbers and percentages for categorical variables.

Table II. The summary of the predictive performances.

Learner	BAC	AUC test	AUC train	Sensitivity	Specificity
LPS	0.57	0.56	0.66	0.47	0.67
CSD	0.69	0.77	0.99	0.63	0.76
Stacked	0.70	0.78	0.99	0.58	0.83

BAC, balanced accuracy; AUC, area under the receiver operating curve; LPS, lagged phase synchronisation; CSD, current-source density; Stacked, CSD and LPS combined.

corresponding receiver operating characteristic (ROC) curves are displayed in Figure 1. The best predictive performance in terms of AUC was achieved by the stacked learner (AUC = 0.78), followed by the CSD alone (AUC = 0.77) and LPS alone (AUC = 0.56). For all classifiers, performances were much higher in the training than in the testing data sets (Supplemental Table 2 and Figure S1 available online).

The LASSO regularisation paths for the CSD and LPS classifiers, which show the size of the regression coefficients at different values of the shrinkage parameter lambda, are shown in Figure 2. The contribution of each CSD measurement in the tuned CSD classifier is displayed in Figure 3. Twenty-one out of 57 predictor variables had non-zero regression coefficients and thus contributed to

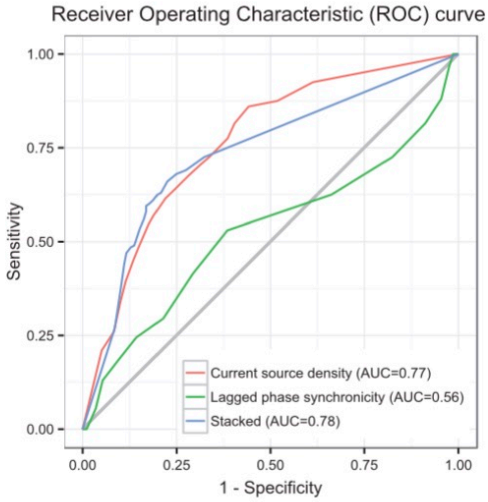

Figure 1. Receiver operating characteristic (ROC) curves for each modality.

the prediction of psychosis. Nine, six and six non-zero coefficients belonged to the gamma, beta1 and beta2 oscillations, respectively. In the gamma band, the three highest contributors were the left inferior parietal lobule (IPL) ($\beta = 3.34$), the precuneus ($\beta = -3.16$) and the right posterior temporal cortex (PPC) ($\beta = -2.44$). In the beta1 band, the highest contributors were the left superior temporal gyrus (STG) ($\beta = 3.79$) followed by the precuneus ($\beta = -3.29$) and the right STG ($\beta = -2.04$). In the beta2 band, the three highest contributors were the left IPL ($\beta = 2.30$), the left superior frontal gyrus ($\beta = 2.12$) and the right frontopolar cortex ($\beta = -1.76$). In the tuned LPS classifier, beta1 contributed the most to the prediction of psychosis ($\beta = 0.62$) followed by beta2 ($\beta = -0.33$) and gamma ($\beta = 0.25$).

Discussion

The main purpose of this study was to investigate whether neurophysiological measurements could help to predict the clinical outcome of patients at-risk for psychosis. In particular, we assessed whether CSD distribution and LPS of neural oscillations across various brain areas could be predictive of a transition to psychosis. This was achieved by submitting CSD and LPS values to the LASSO machine-learning algorithm to identify multivariate patterns of brain activity that predict transition. The model was internally validated using nested 10-fold cross-validation with 10 repetitions to allow honest estimation of the generalisation capacity of the prediction model. In ARMS patients, transition to

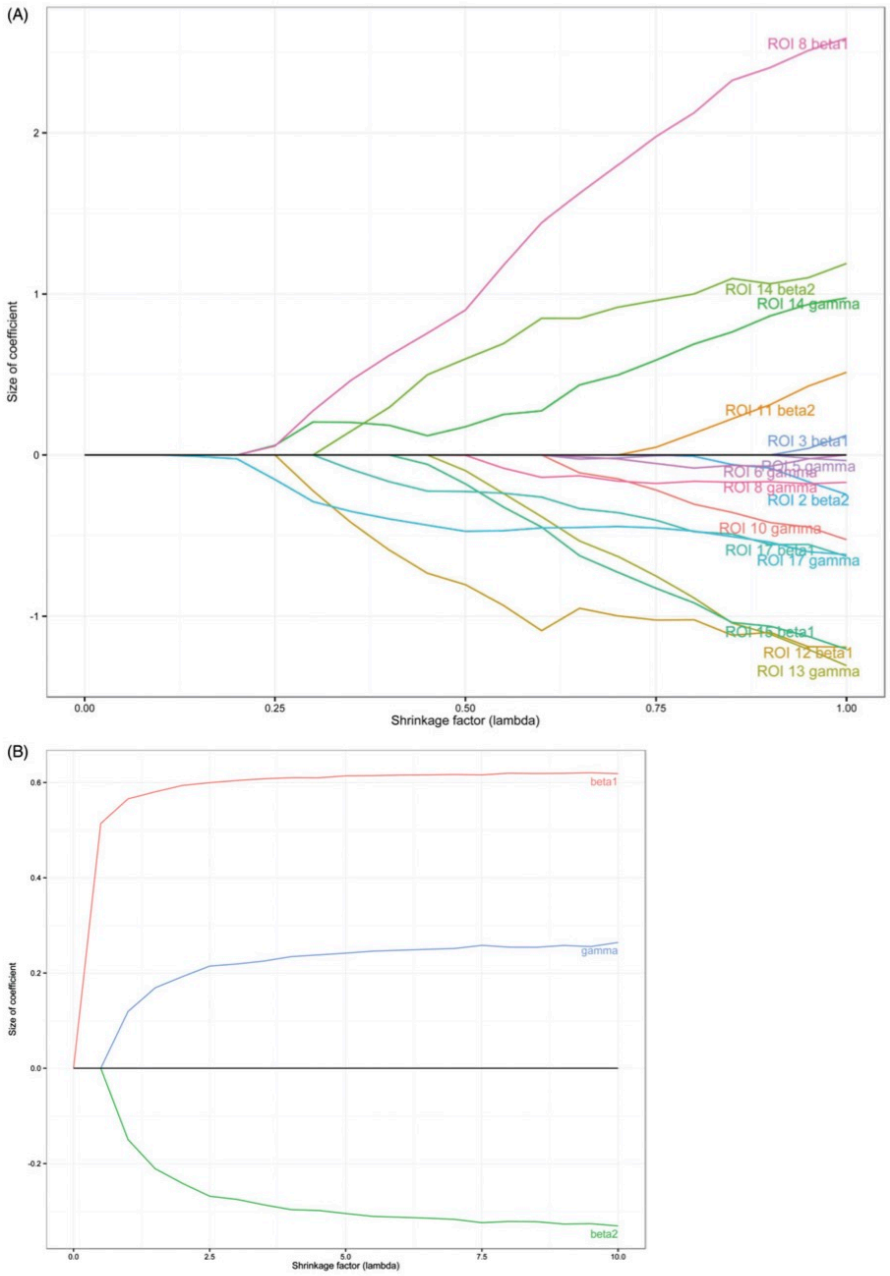

Figure 2. The LASSO regularisation paths for the CSD and LPS classifiers showing the size of the regression coefficients at different values of the shrinkage parameter lambda.

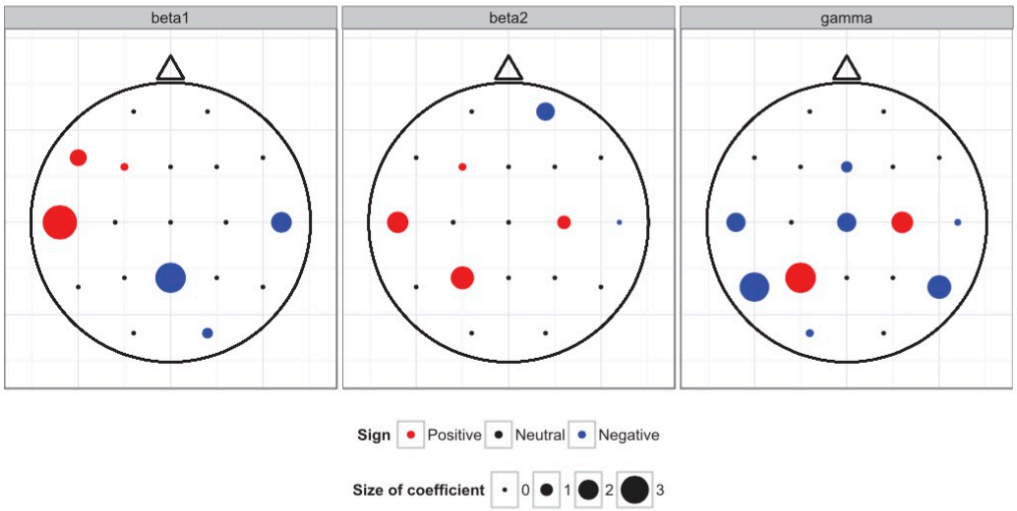

Figure 3. The contribution of each CSD measurement in the tuned corresponding classifier.

psychosis could be predicted with good accuracy from CSD but not from the spatial slope of LPS data. Combining both measures did not improve the predictive accuracy relative to a model that was based on CSD alone. Since ARMS-T and ARMS-NT could not be differentiated in terms of CSD using an univariate approach in our previous study, the findings of this study suggest that whole patterns of CSD have to be taken into account to successfully differentiate these groups. The present study reveals that CSD activity in the left STG, and to a lower extent the right STG in all frequency bands, are important for predicting transition to psychosis. This is in line with previous structural MRI studies showing that predominantly the left STG grey-matter volume is significantly decreased in schizophrenic psychoses (Kasai et al. 2003) and that a decrease in both the left and right STG at baseline, i.e., during the at-risk state, is associated with a later transition to psychosis (Fusar-Poli et al. 2011a). This decrease in grey-matter volume could be the cause of abnormal high frequency oscillations identified in the present study (Uhlhaas and Singer 2010).

The next important ROI identified in our model is the left IPL, whose CSD in both the beta2 and gamma frequency bands are substantially predictive for transition to psychosis. The IPL is a complex brain region involved in attention, time and space integration (Assmus et al. 2003), language, and action processing (Caspers et al. 2013). The IPL has been shown to be a prime candidate in the schizophrenia network disorder and belongs to the cortical regions most affected by disease progression (Torrey 2007). In line with this finding, while an overall decrease in grey-matter volume in IPL has been associated with increased symptoms severity (Wilke et al. 2001), a decrease in the left IPL has mostly been revealed in male patients (Frederikse et al. 2000). These results suggest that patients prone to a later transition could already have abnormal IPL volumes, causing aberrant CSD generation specifically within this cortical region.

Finally, the LASSO algorithm has also identified beta1 oscillations within the precuneus as important predictors. The precuneus is a crucial part of the default-mode network (see Gusnard and Raichle 2001 for review) and has been implicated in a broad spectrum of integrative processes such as self-consciousness, visuo-spatial imagery and social cognition (Cavanna and Trimble 2006). Interestingly, all these processes are known to be impaired in schizophrenic psychoses (Kuhn and Gallinat 2013), which fits well with the hypoactivation and reduction of the precuneus observed in schizophrenic psychoses (Shapleske et al. 2002). Most importantly, grey-matter volumes of the precuneus has also been found to be reduced in ARMS patients with later transition to psychosis (Borgwardt et al. 2008), potentially explaining the here revealed CSD abnormalities of beta1 oscillations in converters.

The three predictors identified in our model could be cortical areas belonging to a particular network already impaired at the risk-state. Interestingly, converging

evidence has revealed that the STG (Salisbury et al. 1998), the IPL (Fusar-Poli et al. 2011b) and the precuneus (Mulert et al. 2004) are all important areas for the generation of the P300 which is an event-related potential component elicited during stimulus evaluation and/or categorisation (van Tricht et al. 2010). Therefore, an alteration of this network could potentially explain why ARMS patients have been shown to have an altered P300 component, a promising biomarker in predicting the progression to full-blown psychosis (van Tricht et al. 2010; van Tricht et al. 2014).

Our study also highlights the importance of internal validation performed to prevent overoptimistic estimates of predictive performance. If we had not cross-validated our model, we would have revealed a near perfect classification with an AUC of 0.99, which, after going through rigorous repeated cross-validations, was decreased to 0.77 (Supplemental Figure S1, training and testing for the CSD analyses, respectively, available online). Unfortunately, in the field of prediction of psychosis, most studies have not applied internal or external cross-validation and therefore are subject to over-optimism (Shah et al. 2013). Furthermore, many of those who did internally cross-validate their results did not do it in line with current recommendations (Steyerberg 2009). That is, they only cross-validated the final model and thus did not take into account the uncertainty introduced by the variable selection.

In many early detection centres for psychosis, resting-state clinical EEGs are now routinely used in the clinical diagnosis of patients exhibiting schizophrenia-like symptoms as a way to search for signs of organic brain disorders such as limbic encephalitis or epilepsy. Moreover, it is relatively easy to place without the need of an advanced degree and only about 15 min of eye-closed acquisition is needed. Automated software could be programmed to perform decent EEG data-preprocessing which would be fed into the model. A prediction score could then be obtained in less than an hour. The latter could be helpful in clarifying the differential diagnosis and in determining the prognosis.

Limitations

It is important to note that – relative to the number of considered predictors – the effective sample size is relatively low. However, it should be noted that ARMS patients are a very difficult to recruit patient population because: (1) these patients are relatively rare, (2) many of them only seek help when they have already developed frank psychosis, and (3) even if they visit our early detection clinic early enough, they often cannot be motivated to participate in scientific studies because they are often already quite suspicious due to the onset of the disease. Due to the small event per variable ratio, we took extra care to prevent over-fitting by conducting repeated nested cross-validation. Nevertheless, our results should be considered preliminary and be replicated in bigger samples. Furthermore, we relied on a low-density EEG system which is commonly used in the clinical field for practical reasons. Although several recent studies have shown that resting-state analyses could reliably be performed using such systems (Babiloni et al. 2013; Canuet et al. 2011,2012), all analyses would have been more precise with a greater number of electrodes. Moreover, some patients across both the ARMS-T and ARMS-NT groups relied on medications other than neuroleptics, which could have influenced the recorded brain activity.

Conclusion

These findings provide preliminary evidence that CSD measurements of high frequency oscillations could be used as predictors for the early detection of psychosis. The main ROIs identified in our model are all important cortical areas in the generation of the P300 ERP component which has been found to be an important predictor of psychosis (van Tricht et al. 2010). To our knowledge, this is the first study to investigate the high frequencies present at numerous ROIs distributed across the brain using powerful neurophysiological techniques. All patients were neuroleptic-naïve and all data were acquired using the widely available low resolution clinical EEG equipment. Moreover, our model was validated using repeated cross-validations which have yielded good internal validation; a step beyond previous EEG studies in the field of early detection.

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Statement of interest

None to declare.

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Publication 3: “Neural Oscillations in Antipsychotic-Naïve Patients with a First Psychotic Episode“

Ramyead et al., 2015

Neural Oscillations in Antipsychotic-Naïve Patients with a First Psychotic Episode

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Abstract

Objectives: In chronic schizophrenic psychoses, oscillatory abnormalities predominantly occur in prefrontal cortical regions and are associated with reduced communication across cortical areas. Nevertheless, it remains unclear whether similar alterations can be observed in patients with a first-episode of psychosis (FEP), a state characterized by pathological features occurring in both late prodromal patients and initial phases of frank schizophrenic psychoses.

Methods: We assessed resting-state EEG data of 31 antipsychotic-naïve FEP patients and 29 healthy-controls (HC). We investigated the 3-dimensional current-source density (CSD) distribution and lagged phase synchronization (LPS) of oscillations across small-scale and large-scale brain networks. We additionally investigated LPS relationships with clinical symptoms using linear mixed-effects models.

Results: Compared to HC, FEP patients demonstrated abnormal CSD distributions in frontal areas of the brain; while decreased oscillations were found in the low frequencies, an increase was reported in the high frequencies (p<0.01). Patients also exhibited deviant LPS in the high frequencies, whose dynamics changed over increasing 3D cortico-cortical distances and increasing psychotic symptoms.

Conclusions: These results indicate that in addition to prefrontal cortical abnormalities, altered synchronized neural oscillations are also present, suggesting possible disruptions in cortico-cortical communications. These findings provide new insights into the pathophysiological mechanisms of emerging schizophrenic psychoses.

Key words: Schizophrenia, Psychosis, EEG, Phase synchrony, Biomarkers

Introduction

Various studies in patients with schizophrenia have investigated the hypofrontality and hyperfrontality hypotheses, which state that these patients have an inability to activate or deactivate frontal regions of the brain.(Guerrero-Pedraza et al. 2012) While some findings on patients with first-episode schizophrenia support the hyperfrontality hypothesis,(Schneider et al. 2007; Whitfield-Gabrieli et al. 2009; Woodward et al. 2009) other studies observed a hypofrontality.(Nejad et al. 2011; Tan et al. 2005) However, most of these studies have made use of fMRI or PET, which do not measure brain activity at different frequency bands, which are known to have distinct dynamical properties, particularly in the schizophrenic brain.(Uhlhaas et al. 2010)

Schizophrenic psychoses are now acknowledged as neurodevelopmental disorders, whose initial signs and symptoms can sometimes be observed as early as in childhood.(Insel 2010) Compared to first-episode schizophrenia, a first-episode of psychosis (FEP) is a state characterized by pathological features occurring in both late prodromal patients and initial phases of frank schizophrenic psychoses,(Sumiyoshi et al. 2008) but do not necessarily fulfill the diagnosis criteria of schizophrenia. Therefore, studies investigating brain abnormalities in FEP patients are clearly needed to bridge the gap between the numerous investigations on patients at-risk for psychosis and those already diagnosed with schizophrenia. In particular, investigations of neural oscillations in FEP patients are rare and those investigating antipsychotics-naïve populations are even scarcer. This is unfortunate as some antipsychotics have been shown to alter low frequency oscillations, particularly in the alpha band.(Centorrino et al. 2014; Kikuchi et al. 2007) Moreover, the few studies on FEP patients assessing resting state EEG lacked a control group(Gschwandtner et al. 2009) or have assessed the EEG only qualitatively.(Manchanda et al. 2003; Manchanda et al. 2008; Manchanda et al. 2014; Manchanda et al. 2005) Other studies used auditory paradigms and demonstrated increased gamma synchronization and reduced global field power in FEP

patients.(Flynn et al. 2008; Valkonen-Korhonen et al. 2003) Thus, in the present study, we investigated a relatively large and rare sample of FEP patients, who had not yet been treated by antipsychotics at time of their clinical EEG session. These patients were recruited by our early detection center for psychosis, ***FePsy***, which has been specially designed to detect and treat emerging psychosis at its very early stages.(Riecher-Rössler et al. 2007) A crucial aim of the current study was to elucidate whether this particular group of patients demonstrates alterations in low and high frequency oscillations. We further aimed to reveal the spatial distribution of these neural oscillations by quantifying reference-free, three-dimensional current source density (CSD) across brain areas. CSD has been shown to be robust against volume conduction while sharpening its spatial resolution.(Nunez et al. 2006)

In addition to an alteration in CSD of neural oscillations, we hypothesize that a disruption of phase-synchronization of neural oscillations across brain areas may be a crucial characteristic of FEP patients. This hypothesis is based on the disconnection hypothesis, which has been described more than ten decades ago and has meanwhile been supported by numerous empirical findings.(Buchsbaum et al. 2014; Schmitt et al. 2011) This hypothesis states that in the schizophrenic brain, cortical regions fail to communicate and synchronize themselves. As these cortico-cortical communications are modulated primarily through phase synchronization,(Fell et al. 2011; Wang et al. 2011) which was found to be impaired in the beta and gamma bands in schizophrenia,(Uhlhaas et al. 2010; 2013) we investigated whether phase synchronization between distributed brain regions is abnormal at different frequency bands in patients with a first psychotic episode. Finally, because phase synchronization plays a crucial role in various cognitive processes,(Doesburg et al. 2008; Ward 2003) we tested the idea that deviant phase synchronizations across cortical areas are associated with positive and/or negative symptoms. To address these questions, we employed a new and non-linear measure of brain connectivity, namely lagged phase synchronization (LPS), which has been shown to be minimally affected by

volume conduction and low spatial resolution (due to the extraction of zero-lag LPS), thus retaining most of the true neurophysiological connectivity.(Pascual-Marqui 2007; Pascual-Marqui et al. 2011)

We hypothesized that in FEP patients, a decrease in oscillatory activity would be observed in some frequencies while an increase would be observed in others. Moreover, we also hypothesized that the LPS across cortical regions would be altered in FEP particularly in frequencies that have been shown to be involved in long-range synchronization (i.e. theta, alpha, beta and not gamma(Uhlhaas et al. 2010)) and that positive and negative symptoms would be associated with these abnormalities.

Methods

Setting and Recruitment

Patients recruited for this study were help-seeking consecutive referrals to the ***FePsy*** Clinic at the University Psychiatric Clinics Basel, which was set up to assess, measure, and treat individuals in the early stages of psychosis.(Riecher-Rössler et al. 2009; Riecher-Rössler et al. 2007) This study was approved by the ethics committee of the University of Basel, and all participants provided written informed consent.

Screening Procedure

The Basel Screening Instrument for Psychosis (BSIP)(Riecher-Rössler et al. 2008), was used to identify FEP patients. The BSIP allows the rating of individuals regarding the inclusion/exclusion criteria according to the PACE criteria(Yung et al. 1998) and has been shown to have a high predictive validity and a good interrater reliability.(Riecher-Rössler et al. 2008) Exclusion criteria for patients includes: age < 18 years, inadequate knowledge of German, IQ < 70 as measured by the Mehrfachwahl-Wortschatz (Test Form A), previous episode of schizophrenic psychosis treated with antipsychotics, psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed depression or borderline personality disorder. We

included FEP patients that were recruited between March 2000 and January 2013 and had a clinical EEG session of at least 15 minutes at baseline assessment.

The FEP patients met the criteria for having transitioned to psychosis according to Yung and colleagues.(Yung et al. 1998) While these patients fulfilled criteria for acute psychotic disorder according to the DSM-IV or ICD-10, they did not necessarily yet meet the criteria of schizophrenia. All FEP patients were antipsychotic and mood-stabilizer naive at time of EEG assessment.

Healthy controls (HC) were recruited from the same geographical area as the patients, through advertisements in trade schools and from the hospital staff. Exclusion criteria for the healthy participants were: history of psychiatric or neurological disease, past or present substance abuse and head trauma.

Assessment of Positive and Negative Psychotic Symptoms

The Brief Psychiatric Rating Scale Expanded (BPRS-E)(Lukoff et al. 1986; Ventura et al. 1993) was used to assess positive and negative psychotic symptoms. The positive psychotic symptom scale was based on the four items hallucinations, suspiciousness, unusual thought content, and conceptual disorganization and the negative psychotic symptom scale was based on the items blunted affect, psychomotor retardation and emotional withdrawal.(Velligan et al. 2005)

EEG Recordings

EEG data were recorded at the University Hospital of Basel. Patients sat in a quiet room during eyes closed resting-state condition for about 20 minutes. Every three minutes and/or at signs of behavioral and/or EEG drowsiness, subjects were asked to open their eyes for a period of 5-6 seconds. EEG data were sampled at 250Hz by 19 gold cup electrodes (Nicolet Biomedical Inc), referenced to linked ears and impedances kept below 5Ω.

Artifact Rejection

EEG pre-processing was performed using Brain Vision Analyzer© 2.0 software (Brain Products GmbH). We processed each EEG in parallel split into two branches, one filtered at 0.5Hz and one at 1Hz. We did so in order to apply the ICA matrix from the most stable signal (1Hz) to the one that conserved the most signal (0.5Hz). Both branches were handled in the same way up to the step that involved re-referencing to the common average. Artifact rejection was performed manually, based on visual inspection, to remove epochs containing extreme ocular artifacts, muscles and/or cardiac contamination and bad signals due to random movements. Biased extended Infomax ICA analyses were then performed for the removal of residual eye movements, eye-blinking, muscles and non-biological components contaminated with high gamma frequencies of 50 Hz and above as measured by Fast Fourier Transform (FFT) of the ICA components (resolution at 1Hz, power μV^2, hanning window length of 10%). After applying the ICA corrected matrix of the data filtered at 1Hz to the one filtered at 0.5Hz, data were re-referenced to common average. A final manual rejection based on visual inspection was performed to exclude remaining artifacts as mentioned above

CSD Analyses

The EEG electrode montage in the present study is in accordance with previous recent studies assessing patients(Babiloni et al. 2013; Canuet et al. 2011b; Canuet et al. 2012; Ramyead et al. 2014) and is considered to allow adequate EEG spatial sampling for the estimation of cortical sources of eyes-closed resting-state EEG rhythms.(Babiloni et al. 2013) Accordingly, the oscillatory rhythms acquired during eye-closed resting-state EEG can be sampled with a relatively low number of electrodes, as opposed to the higher density electrode montage required for observing the functional topography of stimuli-related EEG activity.(Babiloni et al. 2013) Computing the intracortical CSD of oscillatory activity was performed using eLORETA.(Pascual-Marqui 2007; Pascual-Marqui et al. 2011) This was based on EEG data segmented into 2s epochs

(638 2s epochs on average, groups did not differ in number of epochs). The cross-spectra were computed as the average of all cross spectra of each individual EEG epoch.

As opposed to conventional EEG analyses based on voltage, the use of 3D CSD as a measure of brain activity allows for a reliable spatial analysis(Michel et al. 2004) by disentangling the EEG signals from various biological and non-biological artifacts, therefore yielding measures more faithfully representing the neuronal current generators.(Tenke et al. 2011) The neurophysiological imaging technique eLORETA is based on a weighted minimum norm inverse solution procedure which allows for the 3D modeling of the EEG CSD with an exact localization performance, with a high correlation of neural sources that are in close proximity. LORETA has been validated as an efficient and reliable tool to study brain activity by various multi-modal studies. These include neuroimaging studies such as functional(Mulert et al. 2004) and structural MRI,(Worrell et al. 2000) PET(Pizzagalli et al. 2003; Zumsteg et al. 2005) and intracranial EEG recordings.(Zumsteg et al. 2006) As opposed to the first version of LORETA,(Pascual-Marqui et al. 1994) the third iteration eLORETA has no localization bias in the presence of structured noise.(Pascual-Marqui 2007)

eLORETA assumes a head model based on 3 shells (brain, scalp and skull compartments) and the solution space is restricted to the cortical grey matter/hippocampus, which comprises 6239 voxels of 5 mm^3 each. Computing the lead field in the above-mentioned head model is based on the Montreal Neurological Institute brain MRI average.(Mazziotta et al. 2001) CSD analyses were based on the following frequency bands: delta (1.5-4Hz), theta (4-8Hz), alpha1 (8-10Hz), alpha2 (10-13Hz), beta1 (13-21Hz), beta2 (21-30Hz) and gamma (30-50Hz).

LPS Analyses

To compute the phase synchronization, we defined 19 regions of interests (ROIs) spread along the cortex.(Canuet et al. 2012; Ramyead et al. 2014) These ROIs were based on the Montreal Neurological Institute (MNI) coordinates of the cortical voxel (Table S1 and more LPS technical

details in supplementary appendix 1). Activity at centroid voxels for each ROI was extracted. We then computed the LPS between all the 19 ROIs resulting in 171 pairwise combinations. LPS computes the non-linear relationship between each pair after the instantaneous zero-lag contribution has been removed. This results in the elimination of non-physiological artifacts such as volume conduction.(Pascual-Marqui et al. 2011) To assess the phase synchronization in relation to distance, we calculated the Euclidian distance between the first ROI (x1, y1, z1) and the second (x2, y2, z2) using the Pythagorean theorem: $\sqrt{[(x2-x1)^2 + (y2-y1)^2 + (z2-z1)^2]}$ which were then standardized into z-scores.

Statistical Analyses

In order to identify the CSD differences between FEP and HC, we used the statistical nonparametric mapping (SnPM) implemented in eLORETA,(Holmes et al. 1996) which has been validated(Anderer et al. 1998; Pascual-Marqui et al. 1999) and used in previous clinical studies.(Canuet et al. 2011a; Canuet et al. 2012; Ramyead et al. 2014) Differences in cortical oscillary through each frequency band were calculated by voxel-by-voxel independent sample t-statistics with electrode/voxel-wise normalization (relative power type). Subsequently, 5000 permutations were used to perform randomized SnPM and correct for the critical probability threshold across all voxels and all frequencies (1% probability level).

Due to the age difference between the HC and FEP groups (Table 1), we assessed whether age was associated with the deviant oscillatory activity revealed using the methods above. Thus, we extracted CSD values from the global maximum voxel at corresponding frequencies that differed between FEP and HC. Afterwards, their association was assessed by linear regression models using CSD as dependent variables and centered age and diagnostic group as independent variables. In addition to this ROI approach, a brain-wide analysis was performed by correlating voxel-wise age with CSD within eLORETA for each frequency. This whole brain analysis was

based on 5000 permutations to determine the empirical probability distribution for the maximal statistics under the null hypothesis.(Canuet et al. 2012; Hubl et al. 2007)

To assess group differences in LPS, we fitted a linear mixed-effects model using LPS values from 171 pairs as the dependent variable and the centered Euclidian distance (within-subjects) and group (between-subjects) along with their interaction as independent variables. Moreover, the model included an intercept term that randomly varied per individual. To control for heteroscedasticity, we explicitly modeled the variance in the model by adding a constant plus power variance function structure. To examine the association between positive/negative symptoms and lagged phase synchronization as a function of Euclidian distances, we fitted linear mixed-effects models that additionally included the centered BPRS positive and BPRS negative symptom scores as fixed effects. These analyses were repeated for each of the seven different frequencies and were controlled for false discovery rates using the Benjamini-Hochberg method.(Benjamini et al. 1995)

Results

Sample Description

From February 2000 to January 2013, 99 FEP patients and 97 HC have been recruited into the ***FePsy*** study. Of these, only 31 FEP patients and 29 HC had sufficient (at least 15 minutes) clinical EEG data and were antipsychotic and mood-stabilizer naive. Four of these patients were currently on antidepressants and 8 were on tranquilizers. The 68 FEP individuals that could not be included due to not having had an EEG session and/or were already medicated with antipsychotics did not differ from the included FEP individuals with regard to gender, age, years of education, positive and negative BPRS total, positive symptoms scores. The clinical characteristics and demographics of the HC and FEP groups are shown in Table 1. There was a difference in age and a small difference in years of education (all p's < .05).

Source Localization

For illustrative purpose, CSD distributions for each group at each frequency band are present in Figure. 1. Non-statistically, in HC, highest oscillatory activities were found in the alpha2 band (0.55 vs. 0.30μA/mm^2 in HC and FEP, respectively) followed by the delta band (0.43 vs. 0.33μA/mm^2). In contrast, in FEP patients the highest oscillatory activities were in the gamma (0.87 vs. 0.37μA/mm^2 in FEP and HC, respectively) and alpha1 (0.38 vs. 0.38μA/mm^2) bands. Regarding the spatial distribution of CSD, statistical analyses revealed that FEP patients had decreased theta activity in the left anterior cingulate (BA32, global maximum at X=−15, Y=35, Z=20, t=-4.40, p<.01, corrected) and decreased alpha1 activity in the left middle frontal gyrus (BA10, global maximum at X=−30, Y=60, Z=10, t=-4.05, p<.01, corrected). Moreover, FEP patients also had increased activity in the beta2 band bilaterally in the superior frontal gyrus, particularly in the left hemisphere (BA8, global maximum at X=−20, Y=30, Z=55, t=4.23, p<.01, corrected), and increased gamma activity in the left medial frontal gyrus (BA9, global maximum at X=−20, Y=35, Z=25, t=3.75, p< .01, corrected).

CSD and Age

Four Linear regression models with CSD activity, individually extracted at the global maximum voxel from the theta, alpha1, beta2 and gamma frequency bands, as dependent variable and age and group as independent variables revealed no significant main effect of age (all 4 p's>0.80, corrected). A whole brain voxel-wise correlations analysis also demonstrated that age was not associated with CSD measurements for any frequencies (p>.20, corrected).

LPS Analyses

Linear mixed-effects models with LPS values as dependent variables, Euclidian distance, group and their interaction as independent variable and a random intercept per subject revealed significant main effects of Euclidian distance for all frequency bands (p<0.05 for the delta frequency and p<0.001 for all 6 remaining frequencies, corrected). This was due to decreased LPS with increasing distances between the ROIs (171 pairs) in all frequencies except for the delta band

(Figure. S1A, supplementary appendix 1). Moreover, there was a significant interaction between group and Euclidian distance for LPS of beta1 and beta2 oscillations ($p<.05$ and $p<0.001$, respectively, corrected for 7 comparisons), which was due to a stronger decrease of LPS with increasing anatomical distance in FEP patients than in HC (Figure. 3). In the delta and alpha1 frequency bands similar interactions were observed, which however were not significant, possibly due to rigorous correction for multiple comparisons ($p<.10$, corrected, Figure. S1A, supplementary appendix 1).

In the linear mixed-effect models that also included BPRS positive symptoms as an independent variable, a significant second-order interaction between LPS, distance and BPRS positive symptoms in the beta2 frequency bands was revealed ($p<0.001$, corrected), indicating that higher positive symptoms in FEP patients were associated with a particularly strong decrease of LPS with increasing distance, which was exaggerated with increasing positive symptoms (Figure. 4A). Furthermore, the model with negative symptoms revealed a main effect of BPRS negative symptoms on a trend level ($p=0.05$, corrected) and a second order interaction between LPS, distance and BPRS negative solely in the beta1 band ($p<0.001$, corrected, Figure. 4).

Discussion

In this study we investigated whether antipsychotic-naïve first episode of psychosis patients demonstrated deviant CSD and LPS when compared to healthy individuals. We found decreased CSD of theta and alpha1 oscillations in the left frontal cortex, but increased beta2 CSD in fronto-parietal areas and increased gamma oscillations in the left frontal cortex. We additionally found an inverse relationship between LPS and Euclidian distance in the beta1 and beta2 bands, which was stronger in FEP compared to HC individual for beta1 and less strong in FEP compared to HC individual for beta2.

CSD Analyses

This study emphasizes and demonstrates that both a hypofrontality and a hyperfrontality are concurrently present in emerging psychosis. While a hypofrontality in CSD is observed in the low theta and alpha1 frequencies, a hyperfrontality has been revealed in high beta2 and gamma bands. The mid frequencies such as alpha2 and beta1 were not associated with localized abnormal oscillatory activity. These results extend previous studies focusing on cerebral blood flow during rest(Guerrero-Pedraza et al. 2012; Whitfield-Gabrieli et al. 2009) that could not assess activity at different frequency bands.

The revealed abnormality in the theta band specifically in the left anterior cingulate cortex (lACC) is in line with a study, which has revealed that unmedicated patients with a first episode of schizophrenia have higher than normal glutamine levels in the lACC resulting in reduced glutamatergic activity.(Kegeles et al. 2012; Théberge et al. 2002) Deregulations at this location has been shown to alter theta oscillatory activity and working memory.(Holscher et al. 2005) Moreover, ACC theta oscillations in non-human primates have been shown to predict task rules comprehension, adjustments to errors(Womelsdorf et al. 2010) and various other attentional processes,(Tsujimoto et al. 2006) all of which have been shown to be impaired in schizophrenia.(Mesholam-Gately et al. 2009)

Although both the HC and the FEP groups had the same cortical average CSD in the alpha1 frequency band (Figure. 1), FEP patients had significantly lower CSD in the left middle frontal gyrus. Only few studies have reliably revealed deviant frontal alpha oscillations in schizophrenia.(Knyazeva et al. 2008) One potential explanation could be that we investigated the alpha band (8-13 Hz) split into two more refined frequency bands namely alpha1 (8-10Hz) and alpha2 (10-13Hz), which have been shown in healthy human subjects to have different dynamic properties.(Knyazev et al. 2003; Micheloyannis et al. 2006; Mu et al. 2008) Moreover, antipsychotics have been found to normalize oscillations, particularly alpha

oscillations,(Centorrino et al. 2014; Kikuchi et al. 2007) possibly by their antagonistic activity at 5-HT2A receptors,(Kometer et al. 2013) which may explain why we revealed decreased alpha oscillations compared to previous studies assessing antipsychotic-treated schizophrenic patients.

The increased CSD in the beta2 bands on both hemispheres, that is, across both superior frontal gyri, could be due to oligodendrocytes loss that has been reported in patients with schizophrenia in this area(Hof et al. 2003) which play an important role in promoting neural synchrony.(Fields 2008; Schmitt et al. 2011) Furthermore, oligodendrocytes contain NMDA receptors,(Káradóttir et al. 2005) thus, a reduction would also result in reduced NMDA receptor activations and consequently reduced GABAergic inhibition.(Koch et al. 2015) Furthermore, this process has been suggested to increase beta2 oscillatory activity and cortical gamma rhythms.(Koch et al. 2015; Roopun et al. 2008) In accordance with this, the present study also revealed an increase in gamma oscillations in frontal regions.

The increased frontal gamma oscillations in FEP patients is in accordance with several previous studies on schizophrenic psychoses.(Hirano et al. 2015; Uhlhaas et al. 2013) Even though both an increase and a decrease of gamma oscillatory activity have been observed in patients suffering from psychosis, converging evidence suggests that an increase is mostly present in unmedicated patients exhibiting positive symptoms.(Lee et al. 2003) In support of this, a recent study has shown an increase in resting-state frontal gamma activity already in patients at-risk for psychosis who later transitioned to psychosis but not in those who did not.(Ramyead et al. 2014)

Taken together, these findings support the notion that, in first episode psychosis, both hyper- and hypo-activations are present in frontal cortical areas. Alterations in the low frequencies have only been observed in few previous studies.(Gschwandtner et al. 2009; Kim et al. 2015; Knyazeva et al. 2008) One possible reason for this discrepancy is that in the present study only antipsychotic-naïve patients were included, whereas most previous investigations had studied patients under the

influence of antipsychotics, which might have obfuscated the detection of these alterations.(Centorrino et al. 2014; Kikuchi et al. 2007)

LPS Analyses

Our results show that FEP patients demonstrate a stronger decrease in LPS with increasing Euclidian distance in the beta1 band (Figure. 3A) than HC. Furthermore, an inverse association with LPS and Euclidian distance was increased with increasing positive symptoms (Figure. 4A). Surprisingly, the opposite group x distance interaction was revealed in the beta2 band (Figure. 3A) and was associated with negative symptoms (Figure. 4B).

The heightened synchronization among cortical areas closest in proximity, i.e. at low Euclidian distances in relation to LPS values in the beta1 band, could reveal a perturbation of long-range synchronization in the psychotic brain. These findings could be due to altered anatomical connections in terms of cortical thickness and volume in schizophrenia,(Oertel-Knöchel et al. 2013; Pol et al. 2014) which have been shown to alter beta oscillations,(Uhlhaas et al. 2010) thus potentially leading to a poorer communication among numerous cortical areas. Furthermore, these results support the disconnectivity hypothesis, which has been described more than 40 years ago(Beaumont et al. 1973) and is amongst the best supported hypotheses today.(Buchsbaum et al. 2014; Schmitt et al. 2011) Interestingly, our results are in line with a previous study, which revealed that at-risk patients who later developed psychosis had similar deviant LPS in the beta1 band compared to those without later transitions,(Ramyead et al. 2014) thus further supporting that psychoses are indeed developmental disorders and that some deviances in oscillatory rhythms could be observed at a very early stage of the disease.

Limitations

A limitation of this study is that the EEG data was obtained with a relatively low density EEG equipment. Although some recent studies have used a similar system for resting-state source-localization and connectivity measurements,(Babiloni et al. 2013; Canuet et al. 2011b; Canuet et

al. 2012; Ramyead et al. 2014) a higher density system would have yielded more precise results. Moreover, even though all patients were never medicated with antipsychotics and mood-stabilizers, some of these patients were on antidepressants and tranquilizers, which could have had some influence over the results.

Conclusions

Our findings reveal that both a hypofrontality and hyperfrontality are present in antipsychotic-naïve patients with a first episode of psychosis, which are observed in the low and high frequencies, respectively. Moreover, the observed increased lagged phase synchronization across smaller inter-cortical areas in the beta1 frequency may well result in poor communications across the brain and could potentially arise from anatomical abnormalities.

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Statement of Interest

None to declare.

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Table 1: Demographic and clinical characteristics at EEG assessment

	HC N=29	FEP N=31	*p* Value
Gender:			0.815
Women	14 (48.3%)	13 (41.9%)	
Men	15 (51.7%)	18 (58.1%)	
Age	22.4 (5.02)	30.8 (8.92)	<0.05
Years of education	11.9 (1.93)	10.5 (2.99)	<0.05
Antidepressants currently:			
no		27 (87.1%)	
yes		4 (12.9%)	
Tranquilizer currently:			
no		23 (74.2%)	
yes		8 (25.8%)	
BPRS Positive Symptoms		13.4 (3.45)	
BPRS Negative symptoms		5.79 (2.36)	
BPRS total score		55.0 (12.1)	

HC = healthy controls; FEP = first episode of psychosis patients; BPRS = Brief Psychiatric Rating Scale. Categorical and continuous variables were compared by Pearson $\chi 2$ (or Fisher's exact tests if any expected cell frequencies were <5) and ANOVAs, respectively.

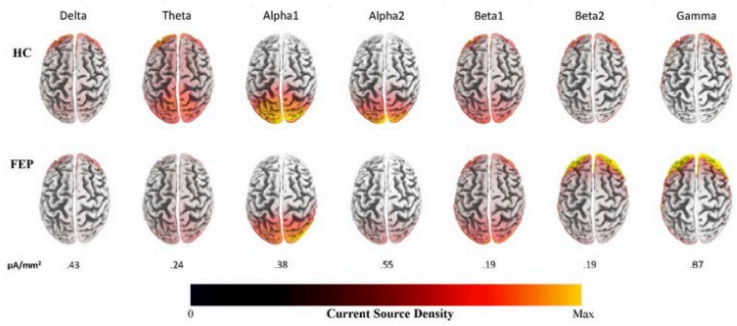
Figure Captions

Figure 1: For illustrative purposes, the average current source density (μA/mm2) by group and frequency bands.

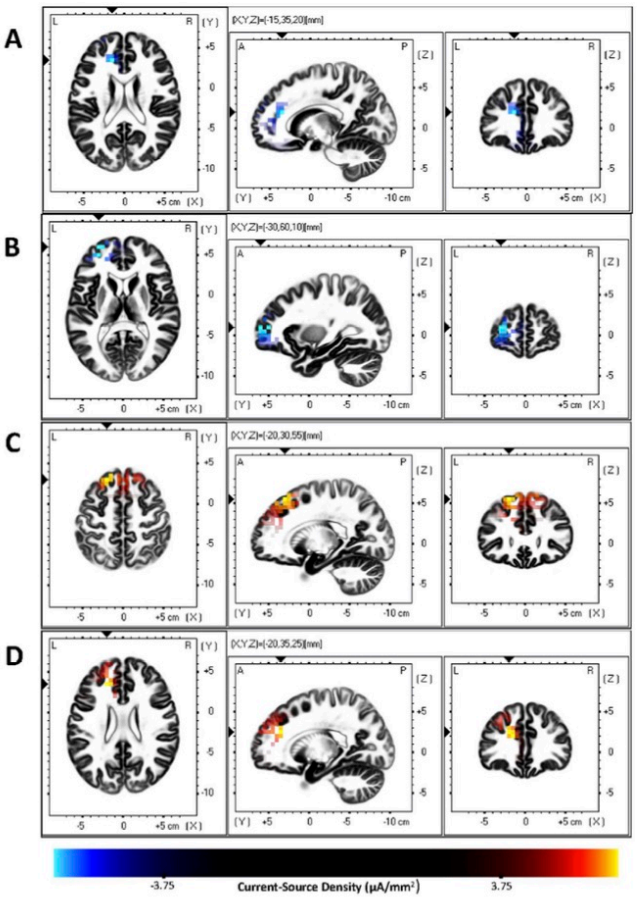
Figure 2: eLORETA statistical map of oscillatory differences in the (A) theta (B) alpha 1 (C) beta2 and (D) gamma frequency bands between FEP and HC.

Figure 3: The lagged phase-synchronization of the (A) beta 1 and (B) beta 2 frequency band as a function of distance. Shaded areas cover regression coefficients with ±1 SE.

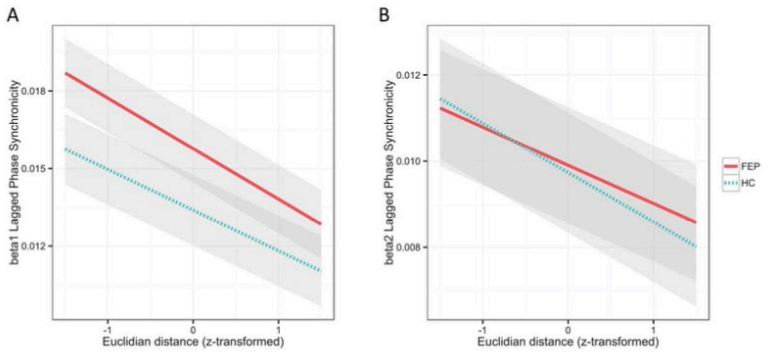
Figure 4: (A) The lagged phase-synchronization of the beta 2 frequency bands as a function of distance for each of 4 different values of BPRS positive symptoms. (B) The lagged phase-synchronization of the beta 1 frequency band as a function of distance for each of 4 different values of BPRS negative symptoms. Shaded areas cover regression coefficients with ±1 SE.



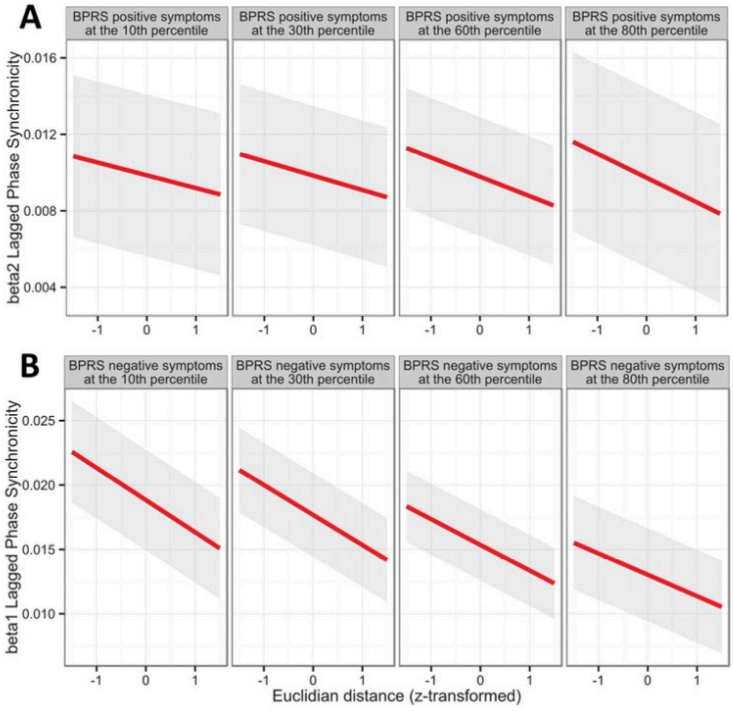
For illustrative purposes only, the average current source density (µA/mm2) by group and frequency bands.



eLORETA statistical map of oscillatory differences in the (A) theta (B) alpha 1 (C) beta2 and (D) gamma frequency bands between FEP and HC.



The lagged phase-synchronization of the (A) beta 1 and (B) beta 2 frequency band as a function of distance. Shaded areas cover regression coefficients with ±1 SE.
627x300mm (72 x 72 DPI)



(A) The lagged phase-synchronization of the beta 2 frequency bands as a function of distance for each of 4 different values of BPRS positive symptoms. (B) The lagged phase-synchronization of the beta 1 frequency band as a function of distance for each of 4 different values of BPRS negative symptoms. Shaded areas cover regression coefficients with ±1 SE.
483x460mm (72 x 72 DPI)

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Supplementary Information

Supplementary Table 1: Montreal Neurological Institute (MNI) coordinates for ROIs used for the current source density and lagged phase synchronization analyses (Canuet *et al.*, 2012, Ramyead *et al.*, 2014).

Number	Regions of Interest (ROIs) within eLORETA	Coordinates (x, y, z)
1	Left frontopolar cortex	-25 65 -5
2	Right frontopolar cortex	25 65 -5
3	Left inferior frontal gyrus	-50 40 -10
4	Left middle frontal gyrus	-45 40 -10
5	Superior frontal gyrus	5 45 50
6	Right middle frontal gyrus	45 40 30
7	Right inferior frontal gyrus	50 40 -10
8	Left superior temporal gyrus	-65 -15 -15
9	Left precentral/postcentral cingulate cortex	-50 -20 60
10	Medial frontal cortex	5 -10 70
11	Right precentral/postcentral cingulate cortex	55 -20 55
12	Right superior temporal gyrus	70 -20 -10
13	Left posterior temporal cortex	-60 -65 -5
14	Left inferior parietal lobule	-40 -70 45
15	Medial parietal (Precuneus)	-5 -65 65
16	Right inferior parietal lobule	45 -70 45
17	Right posterior temporal cortex	55 -70 0
18	Left occipital cortex	-20 -100 10
19	Right occipital cortex	20 -100 5

1.1. Lagged Phase Synchronization Analyses

In technical terms, the LPS analyses calculate the corrected phase synchrony value between signals in the frequency domain based on normalized Fourier transforms yielding a measure of nonlinear functional connectivity. To diminish or eliminate volume conduction and related artifacts, the instantaneous zero-lag contribution has been subtracted from the total phase synchronization yielding only LPS. In other words, the classical overall "squared" phase synchronization, which is highly contaminated by the instantaneous artifactual component, is defined as:

(1)

$$\varphi^2_{x,y}(\omega) = \left|f_{x,y}(\omega)\right|^2 = \left\{\mathrm{Re}\left[f_{x,y}(\omega)\right]\right\}^2 + \left\{\mathrm{Im}\left[f_{x,y}(\omega)\right]\right\}^2$$

with:

(2)

$$f_{x,y}(\omega) = \frac{1}{N_R}\sum_{k=1}^{N_R}\left[\frac{x_k(\omega)}{|x_k(\omega)|}\right]\left[\frac{y_k^*(\omega)}{|y_k(\omega)|}\right]$$

where $x_k(\omega)$ and $y_k(\omega)$ match to the discrete Fourier transforms of the two signals of interest x and y at frequency ω for the k-th EEG. Re[C] and Im[C] denote the real and imaginary parts of a complex number C; the latter explains the cycle of C; and the superscript

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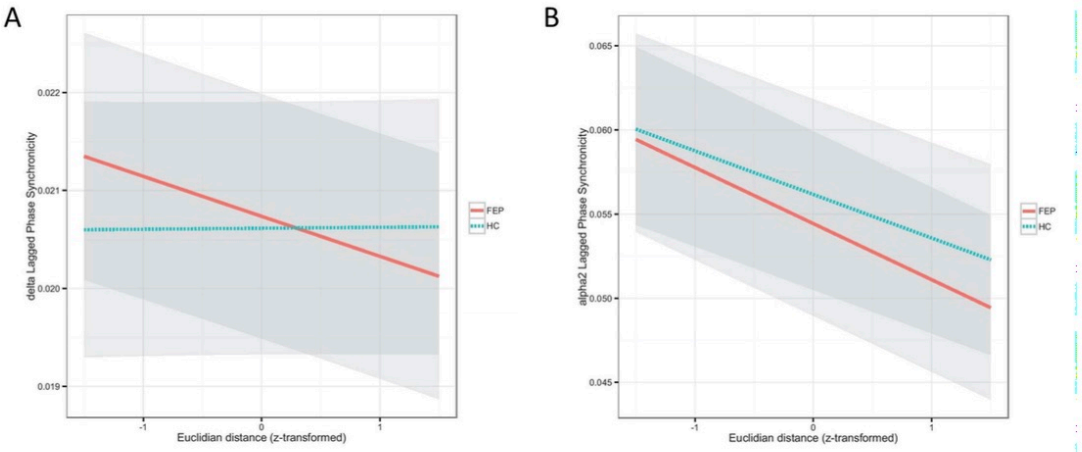
"*", represents a complex conjugate. The instantaneous (zero-lag) connectivity component is narrowly related to the real part of the phase synchronization. LPS, which statistically excludes the instantaneous component of the total connectivity, is defined as:
(3)

$$\varphi^2_{x,y}(\omega) = \frac{\{\mathrm{Im}[f_{x,y}(\omega)]\}^2}{1-\{\mathrm{Re}[f_{x,y}(\omega)]\}^2}$$

Supplementary Figure 1. The lagged phase-synchronization of the (A) delta and (B) alpha 2 frequency band as a function of distance. Shaded areas cover regression coefficients with ±1 SE.



Ramyead et al., 2015

References

Canuet L, Tellado I, Couceiro V, Fraile C, Fernandez-Novoa L, Ishii R, et al. Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. PLoS One. 2012;7(9):e46289.

Ramyead A, Kometer M, Studerus E, Koranyi S, Ittig S, Gschwandtner U, et al. Aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis. Schizophrenia bulletin. 2014.

Discussion

This dissertation has revealed that new, advanced measures of neural oscillations, in conjunction with advanced statistical and computational methodology, are capable of disentangling complex neural oscillatory activity that is predictive of psychosis in at-risk patients. We have revealed that: 1) ARMS-T patients demonstrate abnormal neural oscillations not found in ARMS-NT at baseline; 2) Patterns of abnormal brain activity present in ARMS-T could be detected by machine learning algorithms and allow for the individualized prediction of transition to psychosis with promising accuracy; and 3) FEP patients, the ones who already had an episode of psychosis, demonstrate similar brain abnormalities as ARMS-T at baseline.

Together, these results suggest that neural oscillations are potential markers for the early detection of psychosis that can be assessed using the widely available and routinely applied EEG. This equipment helped us to elucidate that ARMS-T patients demonstrate localized abnormal neural oscillations as well as abnormal phase synchronizations across brain areas. The project entitled “Neural Oscillations in Antipsychotic-Naïve Patients with a First Psychotic Episode” supports these results in a cross-sectional manner by revealing that FEP patients demonstrate similar abnormal neural oscillations and synchrony along with other neural disturbances. In both groups, the abnormal lagged phase synchronization was strongly associated with clinical symptoms, particularly positive ones. These results suggest that a disrupted communication across brain areas could be resulting in the observed psychotic symptoms.

Owing to the revealed neural oscillatory differences between ARMS-T and ARMS-NT patients at baseline, we investigated whether certain patterns of brain activity observed in ARMS-T patients could be identified and thus allow for the prediction of psychosis on

an individualized level. To do so, we employed advanced machine learning algorithms, also known as artificial intelligence, that would be able to train themselves in detecting specific patterns of brain activity. In the project entitled “Prediction of psychosis using neural oscillations and machine learning in neuroleptic-naïve at-risk patients”, we have shown that the so-called Least Absolute and Selective and Shrinkage Operator (LASSO) machine learning algorithm is able to teach itself, merely based on neural oscillations, which patient will later transition to psychosis. We have revealed a promising internally cross-validated predictive accuracy of 78% (using 10-fold repeated cross validations). That is, we were able to predict which ARMS patients would transition to psychosis (ARMS-T) and which ones would not (ARMS-NT) with a correct classification rate of 78%. These findings provide preliminary evidence that neural oscillations can predict the onset of psychosis in at-risk patients. However, it is important to point out that these findings should be replicated in other studies and validated externally.

The field of early detection of psychosis based on multivariate approaches is still in its very early stages. So far, no prediction models in the field have been validated externally. Nonetheless, with the recent completion of data collection by the North American Prodromal Longitudinal Study 2 (NAPLS-2), a multi-site study that gathers data from various domains including EEG and MRI repeatedly over time in a large sample of ARMS individuals, it is only a matter of time until such multivariate analyses are conducted with robust external cross-validation on independent samples. This will furthermore allow to elucidate the changes in neural oscillations based on brain anatomical data over time in patients who later transitioned to psychosis.

Limitations

It is essential to note that - relative to the number of variables included in the machine learning algorithm - the effective sample size is relatively low. Nevertheless, it should be

noted that recruiting ARMS patients is challenging as 1) these patients are relatively rare, 2) many of them only seek help after having already developed frank psychosis, and 3) they frequently cannot be motivated to partake in scientific studies as they are often already quite suspicious due to emergence of the illness. To deal with the small event per variable ratio, we aimed to prevent over fitting by conducting repeated nested cross-validation. All the same, these results should be considered preliminary and be replicated in bigger samples and validated in independent samples. Moreover, we utilized a low-density EEG system which is commonly used in the clinical field for practical reasons. While numerous recent studies have shown that resting-state analyses could reliably be performed using such systems (Babiloni et al. 2013; Canuet et al. 2011; Canuet et al. 2012), all analyses would have been more precise with a larger number of electrodes. Additionally, some patients across both the ARMS-T and ARMS-NT groups depended on medications other than neuroleptics which could have influenced the recorded brain activity.

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Declaration by candidate

I herewith declare that I have autonomously accomplished the PhD-thesis entitled *Predicting Psychosis using Abnormal Neural Oscillations and Synchrony in Conjunctions with Machine Learning Algorithms* ". The thesis consists of original research articles that were written in collaboration with the coauthors enlisted. The articles have been published in peer-reviewed journals except the article "Neural Oscillations in Antipsychotic-Naïve Patients with a First Psychotic Episode ", which is under review. All references used were cited accordingly and only allowed resources were used.

Signature: _____

Date: _____

Curriculum Vitae

PERSONAL DATA

Name:	Avinash Ramyead
Date of birth:	24 April 1989
Citzenship:	Canadian
	Mauritian

EDUCATION

01/1994-09/1999	Loreto Convent Curepipe, Mauritius
01/2000-08/2004	St Joseph College, Mauritius
09/2004-01/2006	Guildford Park Secondary School, BC, Canada
02/2006-06/2007	Sullivan Heights Secondary School, BC, Canada
09/2007-05/2011	University of British Columbia, Vancouver, Canada Bachelor in Psychology
09/2011-02/2013	University of Geneva, Geneva, Switzerland Masters of Science in Interdisciplinary Neuroscience
02/2013-Present	University of Basel, Basel, Switzerland PhD in Psychology

TECHNICAL SKILLS

PhD Project: Neural Oscillations in Emerging Psychosis
Supervisor: Professor Anita Riecher-Rössler, University of Basel, Switzerland
Collaborator: Dr Michael Kometer, University of Zurich, Switzerland

Master's Degree Project: Conducting a combined fMRI + 64 channels MRI-compatible EEG + Bipolar electrodes study
Supervisor: Professor Sophie Schwartz, University of Geneva, Switzerland
Collaborator: Professor Dimitri Van de Ville, Ecole Polytechnique Fédérale de Lausanne, Switzerland

ELoreta: Frequency analysis, Connectivity analysis

EEG: Installing 64 Channels EEG, artifact removal (eye-movements, muscle activity, cardioballistic and magnetic resonance), ICA, ERPs analysis, Time-Frequency analyses

Statistical Analyses: T-test, Anova, Manova, PCA, Cluster Analysis, Discriminant Analysis, EFA, CFA, PCA, Linear Mixed-Effects Models. All performed within the R statistical environment

MRI/fMRI: MRI operator at the Brain and Behaviour Laboratory, University of Geneva

SPM: Spatial preprocessing, creating a design matrix, first and second-level analysis, contrast Analysis

Stimulus Presentation: Matlab (Cogent), E-Prime

Programming Languages: R, Matlab, Java, Visual Basic 6

Operating Systems: Windows XP, Windows Vista, Windows 7, Windows 8, Mac OS X

Miscellaneous: Desktop PC maintenance, repair and upgrade

LANGUAGE SKILLS

French	Excellent written and oral command
English	Excellent written and oral command
Creole	Excellent written and oral command
German	Basic written and oral command

AWARDS/ACHIEVEMENTS

03/2013	Swiss National Research Fund (128'476.00 CHF)
07/2007	President's Entrance Scholarship
05/2007	Second place in BC Provincial "Concours d'art Oratoire"
05/2007	First Place in regional Surrey "Concours d'art Oratoire"
04/2005	Life Savers Level 1, St John Ambulance
03/2005	Introductory Teen Etiquette, Western School of Protocol

04/2003	Gold Medal in Karate/Kick-boxing (full contact) competition

EXPERIENCE

09/2013- Present	Principal investigator of an EEG study on patients with emerging psychosis Supervisors: Professor Anita Riecher-Rössler, Dr Erich Studerus, Dr Michael Kometer
07/2013	Exploring the human mind with brainwaves workshop Bangor University, Wales
09/2011- 02/2013	Simultaneous fMRI + 64 BrainAmps EEG + Bipolar electrodes paradigm to investigate the effects of unfinished business on different types of resting states Supervisor: Dr Sophie Schwartz
09/2012- 12/2012	Observing TMS, TMS + delayed fMRI and TMS + delayed EEG experiments Christoph Michel's laboratory, University of Geneva
06/2009	BC provincial exam marker: Marking the oral component of French Immersion 12 exam BC Ministry of Education
08/2008-05/2011	Donor Supervisor: Helping and monitoring the donor for signs of re-bleed and fatigue Canadian Blood Service
09/2009-12/2009	Volunteer: Interacting with the patients BC Cancer Agency
05/2007-05/2009	Senior Monitor: Monitoring a group of students for French camp Canadian Parents for French

PEER REVIEWED ARTICLES

Published/ In-Press

Ramyead, Avinash, et al. "Aberrant current source-density and lagged phase synchronization of neural oscillations as markers for emerging psychosis." *Schizophrenia bulletin* (2014): sbu134.

Ramyead et al., "Prediction of Psychosis using Neural Oscillations and Machine Learning in Neuroleptic-Naive At-Risk Patients". The World Journal of Biological Psychiatry (2015, in press).

Uttinger et al., "Early detection of psychosis: helpful or stigmatizing experience? A qualitative study". Early Intervention in Psychiatry (2015, in press)
Spitz et al., "Correlations between self- and observer-ratings of psychopathology in at-risk mental state and first episode psychosis patients - influence of disease stage and gender". Early Intervention in Psychiatry (2015, in press).

Ittig, S., et al. "Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects." *European Psychiatry* (2014).

In Review
Ramyead et al., "Abnormal neural oscillations and phase synchronicity in neuroleptic naive patients for psychosis: Association with cortical thickness".

In Preparation
Ramyead et al., "Understanding Working Memory Anomalies in the Prodromal Stages of Schizophrenic Psychoses".

Ramyead et al., "The 5-HT2A/1A Agonist Psilocybin as an Inducer for Deviant Neural Connectivity".

PUBLISHED ABSTRACT

Deviant Neural Oscillations And Lagged Phase Synchronicity In Patients With An At-risk Mental State For Psychosis
Avinash Ramyead, Michael Kometer, Erich Studerus, Martina Papmeyer, Sarah Ittig, Ute Ute Gschwandtner, Peter Fuhr, Anita Riecher-Rössler
Schizophrenia Research 153, S355-S356

The Course Of Cognitive Functioning In Clinical High Risk And First-episode Psychosis Individuals
Martina Papmeyer, Erich Studerus, Marlon Pflüger, Sarah Ittig, Avinash Ramyead, Martina Uttinger, Susan Koranyi, Fabienne Fend, Anita Riecher-Rössler
Schizophrenia Research 153, S352-S353

Deficits In Fine Motor Skills In Emerging Psychosis
Fabienne S Soguel-dit-Piquard, Erich Studerus, Martina Papmeyer, Ittig Sarah, Uttinger Martina, Avinash Ramyead, Susan Koranyi, Anita Riecher-Rössler
Schizophrenia Research 153, S148

Gender Differences In Cognitive Functioning In At-risk Mental State For Psychosis, First-episode Psychosis And Healthy Control Subjects
Sarah Ittig, Erich Studerus, Martina Papmeyer, Martina Uttinger, Susan Koranyi, Avinash Ramyead
Schizophrenia Research 153, S243-S244

UNPUBLISHED RESEARCH PROJECTS

12/2009 Ramyead, A., Ho, E., Song, Y., *The Role Played by the Soil Moisture Regarding the Nesting Site Selection of the Lumbricus rubellus,*

unpublished Laboratory Investigations in Life Science thesis, Department of Zoology, University of British Columbia

11/2010 Ramyead, A., *Elevated Levels of Corticosteroids in Early Life Experiences are Associated With Alzheimer's Disease in the Elderly,* unpublished Behavioral Neurendocrinology thesis, Department of Psychology, University of British Columbia

03/2011 Ramyead, A., *The Neuroprotective Effects of Propofol in Subanesthetics Doses on the Brain,* unpublished Drugs and Behavioral Neuroscience thesis, Department of Psychology, University of British Columbia

11/2010 Ramyead, A., *Cultural difference towards the Occult,* unpublished Cultural Psychology thesis, Department of Psychology, University of British Columbia

02/2013 Ramyead, A., *The Impact of Unfinished Business on Subsequent Ruminations during Wakefulness and Sleep,* Master's Thesis, Faculty of Sciences, University of Geneva

PSYCHOLOGICAL THEORY MODELLING USING COMPUTER PROGRAMMING

10/2010 Simulating Signal Detection Theory

11/2010 Simulating Chaos Theory

11/2010 Simulating Basic Neural Networks

ORAL PRESENTATION

05/2007 *Le Poison Sucré*, the harmful effects of aspartame in mammals, Simon Fraser University, BC, Canada

11/2010 *Effects of Stress and Cortisol on Ageing,* University of British Columbia, BC, Canada

03/2011 *Anaesthetics and the Brain,* University of British Columbia, Canada

09/2012 *The Impact of Unfinished Business on Subsequent Ruminations during Wakefulness and Sleep*, Laboratoire de Recherche en Neuroimagerie, Lausanne, Switzerland

05/2014 *Investigating Emerging Psychosis- A Neurophysiological Approach,* UPK Transfakultäre Forschungskonferenz, Basel, Switzerland

07/2014 *MRI, EEG and laboratory in early detection and differential diagnosis*, FEPSY Symposium, Basel, Switzerland

05/2015 *Abnormal Neural Oscillations in Emerging Psychosis,*
Ecole Polytechnique Fédérale de Lausanne, Switzerland

Poster Presentation

04/2014 *Deviant Neural Oscillations and Lagged Phase Synchronicity in Patients with an At-Risk Mental State for Psychosis*, SIRS Conference Florence, Italy

10/2014 *Abnormal Neural Oscillations and Lagged Connectivity in Patients with First-Episode Psychosis*, SFN Conference, Washington DC, USA