Towards a Neurodynamical Understanding of the Prodrome in Schizophrenia

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ABSTRACT

The identification of biomarkers for the early diagnosis of schizophrenia that could inform novel treatment developments is an important objective of current research. This paper will summarize recent work that has investigated changes in oscillatory activity and event-related potentials with Electro/Magnetoencephalography (EEG/MEG) in participants at high-risk for the development of schizophrenia, highlighting disruptions in sensory and cognitive operations prior to the onset of the syndrome. Changes in EEG/MEG-data are consistent with evidence for alterations in Glutamatergic and GABAergic neurotransmission as disclosed by Magnetic Resonance Spectroscopy and brain stimulation, indicating changes in Excitation/Inhibition Parameters prior to the onset of psychosis. Together these data emphasize the importance of research into neuronal dynamics as a crucial approach to establish functional relationships between impairments in neural circuits and emerging psychopathology that together could be fundamental for early intervention and the identification of novel treatments for emerging psychosis.

KEYWORDS

Schizophrenia, Neuroscience, Prodrome, Oscillations, E/I-Balance, Electrophysiology

1. INTRODUCTION

1.1 Schizophrenia and Prodrome

Schizophrenia is a severe psychiatric disorder that is associated with a life-time prevalence of approximately 1 % that continues to be a significant challenge for efforts to improve outcome and treatment. This is because the pathophysiological processes that give rise to both the psychophathological features (positive, negative and disorganized symptoms) as well as the pronounced cognitive deficits remain to be elucidated (Insel, 2010). Accordingly, current treatment options are largely focussed on targeting symptomatic manifestations once the disorder is fully manifested while interventions that correct fundamental circuit abnormalities remain unavailable.

Current theories have highlighted that one possible reason for the emergence of psychosis and associated perceptual and cognitive deficits is to be found in the disruption of neural dynamics that coordinate brain activity in large-scale networks (Uhlhaas & Singer, 2011). One candidate mechanism for this process is the synchronization of oscillatory responses at both low- (delta [1-3 Hz], theta [3-8Hz] and alpha [8-12 Hz]) and high- (beta [13-30 Hz]/gamma [30-100 Hz]) frequencies that have been associated with a wide-range of cognitive and sensory tasks during normal brain functioning (Buzsaki & Draguhn, 2004; Fries, 2009).

Importantly, evidence has emerged suggesting that ScZ is associated with an impairment in both amplitude and precision of synchronized rhythmic activity (Uhlhaas & Singer, 2010), consistent with alterations in circuit mechanisms in the disorder that give rise to generation of neural oscillations during normal brain functioning (Lewis, Curley, Glausier, & Volk, 2012). Crucial variables for the generation of precise rhythmic activity are the balance between the efficiency of excitation/inhibition (E/I) balance (Sohal, Zhang, Yizhar, & Deisseroth, 2009;

Wang, 2010; Whittington, Traub, & Jefferys, 1995) and the layout of long-range connections, both excitatory and inhibitory, held responsible for the synchronization of spatially segregated cell groups (Engel, Konig, Kreiter, & Singer, 1991; Melzer, et al., 2012). Accordingly, investigations into alterations of neural oscillations may allow a unique opportunity for establishing a translational paradigm, whereby electrophysiological variables can be linked to basic circuit deficits that can guide development of novel treatment options.

Experimental and theoretical data highlighted the contribution of GABAergic interneurons towards the generation of high-frequency oscillations (Wang & Buzsaki, 1996)(Traub et al., 2004). Parvalbumin-positive (PV+) cells are one class of interneurons that have been traditionally involved in the generation of gamma-band oscillations through PV+-mediated feedback inhibition of principal cell activity (Sohal, et al., 2009). More recently, a second class of interneurons that express somatostatin (SST) has been shown to be relevant for the generation of gamma-band oscillations (Veit, Hakim, Jadi, Sejnowski, & Adesnik, 2017) while previous evidence linked SST-cells predominantly to the generation of low-frequency rhythms (Urban-Ciecko & Barth, 2016) .

Moreover, there is evidence for a specific role of glutamatergic inputs to PV interneurons for the generation of coordinated network activity. Carlén et al. (Carlen, et al., 2011) showed that the deletion of the NMDA-NR1 receptors on PV interneurons in mice is associated with an increase in spontaneous gamma-band activity in somatosensory cortex, while gamma-band activity during sensory stimulation was reduced. Similarly, the activation of AMPA-receptors is essential for the emergence of high-frequency activity as indicated by evidence highlighting that a reduction of the GLuR-D receptor leads to a decrease of AMPA-mediated currents in PV interneurons and reduced power of oscillations in the 20–80 Hz range (Fuchs, et al., 2001). However, the relative contribution of both NMDA- and AMPA-Rs towards

high-frequency oscillations remains an open question. One possibility is that NMDA-Rs provide more sustained excitatory drive to PV+ cells (Compte, Brunel, Goldman-Rakic, & Wang, 2000), while AMPAR mediated-EPSCs provide faster excitatory inputs to the interneurons that are a prerequsisite for the generation gamma-band oscillations (Kirli, Ermentrout, & Cho, 2014; Rotaru, Yoshino, Lewis, Ermentrout, & Gonzalez-Burgos, 2011).

Data from post-mortem (Gonzalez-Burgos & Lewis, 2008), genetic (Pocklington, et al., 2015) and animal models of ScZ (Behrens, Ali, & Dugan, 2008; Lodge, Behrens, & Grace, 2009) suggest that pathophysiological processes provide converging evidence that GABAergic and Glutmatatergic neurotransmission is impaired in ScZ. Thus, there are consistent findings for a reduction in transcript and protein-levels of PV+cells across cortical regions in ScZ as well as for reduced levels of the key GABA-synthesizing enzyme GAD67 (for a review see (Lewis, Hashimoto, & Volk, 2005)). It is currently, unclear, however, whether the alterations in GABAerig neurotransmission are a primary impairment or whether these alterations are secondary deficits in excitatory pyramidal cells (Lewis, et al., 2012). Moreover, it is conceivable that other variables, such as oxidative stress, may lead to downstream deficits in PV+ cells. Steullet et al. (2017) examined several animal models characterized by either genetic and/or environmental risk-factors in relationship to PV+ cells and oxidative stress. Across all animal models, oxidative stress was negatively correlated with the integrity of PV+ cells.

Further evidence for a dysregulation of E/I-balance in ScZ parameters comes from studies that have examined Glutamate and GABA-levels with Magnetic Resonance Spectroscopy (MRS). The earliest MRS-studies were focusing mainly on high concentration brain metabolites such as N-Acetylaspartic acid (NAA), creatine (Cr) and choline (Cho) (Jessen et al., 2006; Wood et al., 2010; Yoo et al., 2009). More recent efforts have been directed

primarily at measures of GABA, Glutamate or Glutamate + Glutamine (Glx) (P. Fusar-Poli 2011; Kegeles et al. 2012; Tandon et al. 2013; Natsubori et al. 2014; Liemburg et al. 2016; Fuente-sandoval et al. 2015; Menschikov et al. 2016; Modinos et al. 2017). Across studies, elevated glutamate-levels have been demonstrated in cortical and subcortical regions in clinical high-risk (CHR)-participants (Merritt, Egerton, Kempton, Taylor, & McGuire, 2016) while the pattern of changes GABA-levels is inconsistent (Egerton, Modinos, Ferrera, & McGuire, 2017). As MRS-measures of GABA and glutamate could provide important insights into alterations in E/I-balance parameters in ScZ, the combination with EEG/MEG-parameters is potentially informative about the physiological origin of impairments in neural dynamics in ScZ.

1.2 Towards Pre-Emptive Psychiatry and Biomarkers for Early Intervention

Recent efforts in ScZ-research have focussed on the possibility of identifying individuals who have a high risk of developing psychosis and the development of appropriate strategies for risk prediction and early intervention (Fusar-Poli, et al., 2013; McGorry, et al., 2009). This approach is based on long-standing evidence that the manifestation of ScZ is preceded by a prodromal period of up to 5 years during which subtle behavioural changes, cognitive impairments and sub-threshold psychotic symptoms emerge (Klosterkotter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Yung & McGorry, 1996). As a result, clinical high-risk criteria (CHR) have been developed based on the presence of attenuated psychotic symptoms (Yung, et al., 2005) as well as self-experienced perceptual and cognitive anomalies, representing the earliest manifestation of psychosis risk (Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkotter, 2010). Recent data from several high-risk studies have shown that CHRs are associated with transition rates between 10 and 30% over a two year

period (Fusar-Poli, et al., 2013). While screening procedures are characterized by sufficient diagnostic accuracy to detect at-risk individuals (Fusar-Poli, et al., 2015), clinical criteria are currently not sensitive and specific enough to predict psychosis-risk on an individual level, a key objective for early intervention research. Accordingly, biomarkers may be required to boost prediction and allow insights into the underlying neurobiology of the at-risk state that could guide the search for targeted interventions.

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The search for biomarkers has so far focussed on anatomical parameters, such as volumetric studies of grey matter (GM), that have revealed reductions in several brain regions prior to the onset of psychosis in CHR-participants that predict transition to ScZ (Koutsouleris, et al., 2009; Pantelis, et al., 2003). This view is consistent with the hypothesis that developmental perturbations of synaptic pruning may give rise to the onset of psychosis (Feinberg, 1982). In addition, structural magnetic resonance studies of white-matter volume and organization (Carletti, et al., 2012) as well as functional magnetic resonance imaging (fMRI) (Anticevic, et al., 2015) have provided data supporting the hypothesis that anatomical and functional large-scale networks are disrupted prior to psychosis-onset.

A limitation of these approaches, however, is the absence of direct measurements of neuronal activity that provide sufficient temporal resolution as well as the difficulty of relating such measures to basic circuit mechanisms, a prerequisite for translational research (Uhlhaas & Singer, 2012). In the current paper, we will outline the rationale for applying electrophysiological techniques, such as electro/magnetoencephalography (EEG/MEG), in

combination with brain stimulation and MRS to identify novel biomarkers for early diagnosis and interventions in ScZ. In the first part of the paper, we will discuss the evidence for changes in neural oscillations and event-related potentials/fields (ERP/ERFs) in CHR-participants followed by studies with transcranial magnetic and direct current stimulation (TMS/tDCS). In the second part, evidence on changes in GABA and Glutamatergic neurotransmission will be reviewed that are relevant for understanding changes in E/I-balance alterations as causative factors in emerging psychosis. Finally, we will provide an assessment of the current evidence on changes in neuronal dynamics in the prodrome of ScZ with recommendations for future work and links with pre-clinical research.

2. Electrophysiology of the Prodrome

2.1 ERPs in CHR-Participants

ERPs/ERFs are time-locked brain responses to internal or external stimuli and provide a non-invasive method to identify neural correlates of cognitive and perceptual processes (Luck 2012) (for a review of ERP-findings in CHR-participants see Bodatsch et al., 2015). Several ERP/ERF components have been studied extensively in patients with ScZ to gain insights into dysfunctions of basic sensory and higher cognitive processing. Evidence shows that there are impairments in ERP/ERFs at early latencies, such as in the P50 (Bramon et al. 2004), N100 (Ford et al. 2014), P100 (Earls, Curran, & Mittal, 2016) and mismatch negativity (MMN) (Umbricht and Krljes 2005), that have been linked to deficits during the encoding of information, while impairments in the P300 (Bramon et al. 2004), for example, likely reflect failures in higher cognitive processes.

One potential biomarker for psychosis is the auditory MMN or its magnetic counterpart MMNm, an ERP/ERF that is elicited automatically by a violation of a previously established auditory regularity (Näätänen et al. 2007; Näätänen, Gaillard, and Mäntysalo 1978). Current evidence suggest that N-methyl-D-aspartate receptors (NMDA-R) (Javitt et al. 1996) as well as STS-expressing interneurons play a major role in the generation of MMN-responses (Hamm & Yuste, 2016).

In ScZ, MMN amplitudes are consistently reduced across a range of stimulation protocols (for a review, see Umbricht and Krljes 2005) and have been associated with a reduction in both cognition and social functioning (Baldeweg and Hirsch 2015; Light and Braff 2005). Evidence from computational modeling and EEG/MEG-data suggests that dysfunctional predictive processes may underlie MMN-deficits (Sauer et al. 2017; Rentzsch et al. 2015; Wacongne 2015).

Several recent studies investigated MMN-responses in CHR-participants, indicating impaired MMN responses to duration and frequency deviants (Atkinson et al., 2012; Carrion et al., 2015; Hsieh et al., 2012; Jahshan et al., 2012; Koshiyama et al., 2016; Perez et al., 2014b; Shaikh et al., 2012; Shin et al., 2009; Solis-Vivanco et al., 2014). However, not all studies have confirmed this finding (Brockhaus-Dumke et al. 2005; Bodatsch et al. 2011; Mondragón-Maya et al. 2013; Higuchi et al. 2013) and there is evidence to suggest that MMN-deficits are primarily observed in CHR-participants who transition to psychosis (CHR+) (Higuchi et al. 2013; Shaikh et al. 2012 but see Atkinson et al. 2017 for a different finding.)

In addition to MMN-impairments, sensory gating, a pre-attentive measure of auditory processing that involves presentation of two clicks within a 500 ms window, has been consistently found to be impaired in ScZ (Brockhaus-Dumke, et al., 2008). There is an established link between P50 sensory-gating and cholinergic neurotransmission as reflected

by genetic data linking the α-7 nicotinic receptor and P50 responses (Martin & Freedman, 2007).

The auditory N100 has also been utilized to explore sensory gating deficits in ScZ. Currently, there is mixed evidence for P50 and N100 sensory gating deficits in CHR-participants, with some studies reporting evidence for a reduction (Brockhaus-Dumke et al. 2008), while others could not distinguish CHR from both ScZ-patients and controls (van Tricht et al. 2015; Hsieh et al. 2012; Shin, Kim, et al. 2012). Moreover, conflicting findings exist on the predictive utility of P50 and N100 measures for distinguishing CHR+ (converter) from CHR− (non-converter) participants (Brockhaus-Dumke et al. 2008; van Tricht et al. 2011; van Tricht et al. 2015; Shaikh et al. 2015).

In addition, there is an increasing interest to explore sensory attenuation of ERPs/ERFs and by calculating the N1/P1 difference between experimental conditions that involve passive sensory stimulation and an active condition during which the incoming stimulus is self-generated (Cao, Thut, and Gross 2017; Hughes and Waszak 2011). Impaired auditory sensory attenuation has been observed in ScZ and is thought to be related to impaired corollary discharge processes which lead to certain clinical symptoms, such as delusion of control or hallucinations (Ford et al. 2014; Perez et al. 2012). Perez et al. (Perez et al. 2012) explored N1 suppression in CHR-participants and found that the degree of N1 suppression was intermediate between the healthy controls and ScZ-patients. Deficits in the auditory N1 in CHR-participants have been also related to cortical thinning in auditory regions (Shin, Jung, et al. 2012).

In addition to auditory processing, there is increasing evidence for impaired early visual information processing in ScZ patients as reflected by reductions in the P100 (Earls, Curran, and Mittal 2016; Sehatpour et al. 2010) and N170 (McCleery et al. 2015). In CHR-

participants, there is currently only preliminary evidence for reduced P100 and N170 amplitude during face processing (Wölwer et al. 2012).

The P300 is a positive waveform which has been was identified with cognitive processing (Polich & Kok, 1995), such as attention and memory updating. The P300 is modulated by multiple neurotransmitter systems (Huang, Chen, and Zhang 2015), predominantly GABAergic (Watson et al. 2009) and dopaminergic neurotransmission (Pogarell et al. 2011). There is emerging evidence that CHR-participants are characterized by a deficit in the amplitude of the auditory P3a (Atkinson, Michie, & Schall, 2012; Bramon, et al., 2008; Mondragón-Maya, et al., 2013; Nagai, et al., 2013) that is associated with an increased risk for developing psychosis (Kim, Lee, Lee, Kim, & Kwon, 2015). Besides the auditory P300, there is preliminary evidence for a reduction of the visual P300 in CHR participants as well (Lee, Namkoong, Cho, Song, & An, 2010).

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2.2 Neural Oscillations in CHR-Participants

Spectral signatures of EEG/MEG-data have gained increasing interest as a potential biomarker in CHR-participants. One approach has been the analysis of resting-state activity. A robust finding in established ScZ is the increase of slow-wave activity as reflected by elevated delta and theta-band power (Ranlund et al., 2014; see Boutros et al., 2008 for a meta-analysis;) and increased connectivity (Andreou, et al., 2015).. In CHR-participants, findings from several EEG-studies have failed to observe similar effects (Wuebben and Winterer 2001; Lavoie et al. 2012; Ranlund et al. 2014)(Andreou, et al., 2015). However, there is preliminary evidence that CHR+ participants are characterized by elevated frontal delta, theta- and beta-band power that correlates with increased negative symptoms, a pattern

that was not observed in the CHR- group that did not develop schizophrenia (Van Tricht et al., 2014). Moreover, alpha power and alpha peak frequency of resting-state oscillations is reduced in CHR+ (Van Tricht et al. 2014).

Resting-state activity at beta- and gamma-band frequencies was investigated by Ramyead and colleagues (2015) who showed that current source density (CSD) estimates of 30-50 Hz was higher in CHR+ as compared to control participants. Moreover, the authors observed decreased phase synchrony of beta oscillations in the CHR+ group as compared to controls and a CHR- group. In further analyses, it was found that increased beta/gamma CSD-estimates strongly contributed to the prediction of psychosis in CHR-participants (Ramyead et al. 2016).

Moreover, analysis of microstates has been applied to resting-state EEG-recordings. EEG-microstates can be used to identify short (~ 80-100 ms) quasi-stable brain states through considering topographies of ongoing electric potentials (Khanna et al., 2014). There are four standard classes of microstate topography and they have been shown to relate to fMRI resting-state networks (Koenig et al., 2002; Britz et al., 2010). Previous studies have reported alterations in resting-state EEG microstate parameters in ScZ patients compared to healthy controls (for a review see e.g. Rieger et al., 2016), suggesting disturbed information processing in ScZ patients (e.g. Lehmann et al., 2005). A recent study reported altered EEG resting-state microstate characteristics in CHRs compared to healthy controls, suggesting that aberrant resting-state microstates might indicate an increased risk of developing psychosis (Andreou et al., 2014).

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In addition to resting-state activity, recent studies have examined task-related oscillatory signatures in CHR-participants. An MEG-study by Koh et al. (2011) reported reduced alpha event-related desynchronization (ERD) to target tones during an auditory oddball task in 17 CHR individuals. Similar findings were obtained with EEG by Kayser et al. (2014) who observed a reduction in alpha-ERD that was markedly pronounced in CHR+ participants.

High-frequency oscillations have been investigated in the auditory domain in CHR-participants. Recent studies have shown evidence for a reduction in auditory evoked gamma-band responses (Perez et al. 2014; Leicht et al. 2016). Moreover, there is evidence for reduced power and phase-synchronization during auditory steady state responses (ASSRs) in ScZ, in particular to 40 Hz stimulation (Thuné et al. 2016). A recent study by Tada and colleagues (2016) assessed 40 Hz ASSRs in 15 CHR individuals, 13 First-Episode (FEP)-patients and 12 healthy controls, indicating reduced power and phase-locking in CHR-participants.

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2.3 TMS/tDCS in CHR-Participants

Noninvasive brain stimulation techniques such as TMS and tDCs are increasingly being used as tools for investigating the pathophysiology of ScZ (see Agarwal et al. 2013, for a review). One approach to assess changes in E/I-balance parameters in ScZ is the investigation of cortical inhibition through TMS in the motor cortex. Short-latency intracortical inhibition (SICI) assesses intracortical excitability and inhibition by delivering two stimuli (paired pulses) in a condition-test paradigm and has been associated with the activity of $GABA_A$ receptors (Ziemann 2004; Ziemann et al. 2015). In ScZ patients, there is consistent evidence for a reduction in SICI, suggesting a disinhibition of motor cortex (Bunse et al. 2014).

The Contralateral Silent Period (CSP) refers to a sustained decrease in muscle activity found after single pulse (TMS) stimulation of the motor cortex during active contralateral muscle contraction and is mediated by $GABA_B$ receptors (Werhahn et al. 1999). Several studies have indicated abnormalities in CSP in ScZ but the direction of the results is conflicting, with some evidence presented of shortened CSP (Eichhammer et al. 2004; P B Fitzgerald et al. 2002; Paul B Fitzgerald et al. 2002), other results showing prolonged CSP (Wobrock et al., 2009; Bajbouj et al., 2004; Soubasi et al., 2010).

Finally, short-term effects of anodal Transcranial direct current stimulation (tDCs) have been used to examine non-invasively long-term-potentiation (LTP) or long-term-depression (LTD) (Brunoni et al. 2012; Liebetanz et al. 2002). In a recent study by Hasan and colleagues (Hasan et al. 2011), anodal tDCs-induced plasticity was monitored by TMS-generated motor-evoked potentials (MEP) in a group of recent-onset and chronic ScZ -patients. ME-schizophrenia patients showed significantly reduced LTP-like plasticity compared to RO-patients and healthy controls.

First evidence for alterations in TMS-mediated inhibition parameters in CHR-parameters was reported by Hasan et al. (2012) who examined SICI and CSP. CHR-participants as well as FEP-patients showed a reduced SICI response compared to controls, but only the FEP-group demonstrated a prolonged CSP duration. Thus, it was concluded that $GABA_A$-mediated processes (linked to SICI) are disturbed earlier in the disorder than $GABA_B$-mediated mechanisms (linked to CSP). A more recent study by Tang et al. (2014) showed that medicated ScZ-patients demonstrated both prolonged CSP as well as attenuated SICI, whereas CHR-participants only showed prolonged CSP.

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3. Magnetic Resonance Spectroscopy in CHR-Participants

MRS studies of glutamate in ScZ found elevated levels of glutamate or Glx, with significant increases reported in the thalamus, medial temporal lobe, the basal ganglia (Merritt et al. 2016; Poels et al. 2014) and medial prefrontal cortex (Poels et al. 2014). These increases in glutamate are consistent with findings of NMDA receptor hypofunctioning in vivo (Nakazawa, Jeevakumar, and Nakao 2017).

Similar findings have been reported in studies focusing on glutamate or Glx in CHR-participants (Merritt et al. 2016). Significant increases in Glx were found in the medial prefrontal cortex (Fuente-sandoval et al. 2015), caudate (Fuente-Sandoval et al. 2011; Tandon et al. 2013) and thalamus (Tandon et al. 2013). However, decreased glutamate levels have been reported in the thalamus (P. Fusar-Poli 2011) or no difference in glutamate or glx concentrations (Natsubori et al. 2014; Wood et al. 2010; Yoo et al. 2009).

So far, ^{1}H-MRS measures of GABA in ScZ have been inconclusive in established ScZ (Wijtenburg et al. 2015; Egerton et al. 2017). A recent meta-analysis by Egerton and colleagues (2017) suggested that across studies, there is no evidence for change in GABA-levels. However, it should be note that changes have been observed that support either an increase (Kegeles et al. 2012; Tayoshi et al. 2010; Öngür, Prescot, and McCarthy 2010; Rowland et al. 2013) or a decrease of GABAergic neurotransmission (Marenco et al. 2016; Menschikov et al. 2016; Yoo et al. 2009). Differences between studies could potentially be attributed to methodological parameters, illness-stage as well as selection of ROIs.

Accordingly, increases in GABA-levels similar to those observed in ScZ have also been seen in the medial prefrontal cortex and dorsal caudate of CHR-participants (Fuente-sandoval et al. 2015). In contrast, Menschikov et al. reported decreased GABA and a decreased

GABA/Glx ratio in left anterior cingulate cortex of CHR-participants (Menschikov et al. 2016).

4. Discussion

The development of insights into circuit changes that underlie the emergence of psychosis and cognitive deficits in ScZ remains one of the most urgent challenges in mental health research. This is because of limited progress in recent decades in the development of novel interventions that improve outcome in the majority of ScZ-patients. Accordingly, the possibility to identify at-risk individuals prior to the onset of psychosis could potentially allow the delay or even prevention of the full expression of psychosis and associated disability if treatments become available that target mechanisms underlying the development of ScZ.

The current paper aimed to provide a comprehensive overview on neuronal dynamics in at-risk individuals for psychosis to establish whether alterations in neural oscillations and ERPs/ERFs and underlying generating mechanisms are already present in CHR-participants. Evidence has emerged that the pronounced cognitive dysfunctions as well as certain clinical symptoms in ScZ may be the result of aberrant communication between and within neuronal assembles that can be captured through electrophysiological measurements of neural oscillations and event-related fields (Stephan, Friston, & Frith, 2009; Uhlhaas & Singer, 2010). Moreover, such disturbances are thought to be the consequence of alterations in E/I-balance parameters which are important aspects for proper gating of information during normal brain functioning (Haider and McCormick 2009) and for the generation of high-frequency oscillations (Sohal et al., 2009; Whittington, et al., 1995). Importantly, these parameters also allow mechanistic insights into the origin of these circuit dysfunctions

through links with pre-clinical research and thus offer opportunities for the development of novel, more effective and pre-emptive interventions (Uhlhaas & Singer, 2012).

4.1 Neural Dynamics and Biomarkers for Prediction

A crucial prerequisite for this endeavour is the identification of biomarkers that allow on the one hand insights into the causes of emerging cognitive deficits and psychosis and, on the other hand, are suitable for risk-stratification at the individual level to predict clinical outcomes. This is because the current criteria for the diagnosis of CHR-status convey risk for a range of mental health outcomes in young people, including ScZ, affective disorders, personality disorders (Lin, et al., 2015). Moreover, a substantial number of individuals fulfilling CHR-criteria will remain without any symptomatic complaints, highlighting the need to improve on current risk-prediction that is largely based on clinical measures.

Novel algorithms that combine clinical, demographical and neuropsychological information have shown that risk-prediction can be significantly improved over existing data that largely rely on information based on clinical information alone (Cannon, et al., 2016). Accordingly, it remains an open question whether biomarkers obtained through EEG/MEG-parameters perform significantly better or enhance risk-algorithms if they are combined with clinical and neuropsychological data.

Among the most consistent findings in CHR-participants are abnormalities in pre-attentive auditory processing as reflected by the MMN-potential which may also predict onset of psychosis (for a review see Bodatsch et al., 2015). Oscillatory activity has been examined in both task-related and spontaneous contexts in CHR-participants. Reductions in gamma-band activity during auditory stimulation have been reported (Leicht et al., 2016; Perez et al., 2014a, Tada et al., 2016) that replicate a large body of work in established ScZ, indicating that neural circuits are impaired in the generation of high-frequency oscillations (Grent-'t-

Jong, et al., 2016; Kwon, et al., 1999; Spencer, et al., 2004). However, it is currently unclear whether auditory gamma-band oscillations are potential predictors for psychosis development. Preliminary data from resting-state oscillations suggests that aberrant, spontaneous high-frequency oscillations potentially indicate a higher risk for transition to psychosis (Ramyead et al. 2015, 2016), but further data are required to replicate this findings.

An important test therefore of the framework proposed here are further studies into the ability to predict clinical outcome in CHR-participants using time-frequency and ERP/ERF-data. Currently, only a relatively small amount of studies have tested the possibility of predicting psychosis-onset based on information from the EEG/MEG-parameters, especially in regards to the possibility of using neural oscillations as a biomarker for the prediction of psychosis in CHR-groups.

4.2 Circuit Dysfunctions and the Pathophysiology of the Prodrome

Emerging evidence from MRS and brain stimulation highlight that the disruption of ERPs and neural oscillations could potentially be due to alterations in E/I-balance parameters. This is supported by reduced inhibitory cortical transmission as revealed by TMS/tDCS (Hasan et al. 2012; Tang et al. 2014) as well as by elevated Glutamate levels in MRS-measurements in CHR-participants cortex (Fuente-sandoval et al., 2011, 2015; Tandon et al., 2013), suggesting that emerging cognitive deficits as well as psychosis could result from disturbances in GABAergic and Glutamatergic neurotransmission.

This hypothesis is consistent with impairments in MMN-deficits in CHR-participants (Bodatsch, Brockhaus-Dumke, Klosterkotter, & Ruhrmann, 2015) that together with the extensive evidence from studies into established ScZ (Erickson, Ruffle, & Gold, 2016) suggests that the MMM and its neuromagnetic counterpart constitutes currently one of the

most promising biomarkers for ScZ. Among the generating mechanisms that have been implicated in MMN-parameters, involvement of NMDA-Rs (Javitt, Steinschneider, Schroeder, & Arezzo, 1996) as well as SST-interneurons (Hamm & Yuste, 2016) have been demonstrated.

A related finding that points towards circuit anomalies in auditory regions in CHR-participants is the emerging evidence on the failure to generate gamma-band oscillations (Tada, et al., 2016). Given the mechanistic role of PV+ interneurons in the emergence of rhythmic activity at gamma-band frequencies (Sohal, et al., 2009), an obvious candidate mechanism are the impairments in GABAergic neurotransmission. As highlighted previously, however, it is currently unclear whether dysfunctions in PV+ interneurons represent a primary pathophysiological process or a downstream consequence of deficits in excitatory pyramidal cell activity and/or oxidative stress (Lewis, et al., 2012; Steullet, et al., 2017).

This question also highlights that it will remain challenging to develop mechanistic insights into the origins of circuit dysfunctions in ScZ based on non-invasive electrophysiology, neuroimaging and brain stimulation data alone. This is because the disruptions in neural oscillations and ERP/ERF-parameters may represent endpoints of developmental disturbances that can arise from different etiologies. Accordingly, it is imperative that EEG/MEG-approaches are integrated with basic in-vitro and in-vivo studies into the origin and mechanistic role of E/I-balance disturbances in order to arrive at a neurobiologically informed understanding of cognitive dysfunctions and emerging psychosis.

4.3 Neurodynamics and the Treatment of Prodromal Schizophrenia

This approach could offer a novel approach towards the treatment of ScZ that so far has

largely relied on the assumption that dopaminergic abnormalities are leading to psychosis and certain cognitive impairments (Howes & Kapur, 2009). However, given the fact that antipsychotic treatments have not substantially improved the more fundamental cognitive deficits nor negative symptoms of the disorder, it is possible that addressing alternative circuit mechanisms that are crucial for neuronal dynamics has great potential for advancing treatment and therefore clinical outcomes.

Preliminary evidence from a study by Kantrowitz et al. (2015) suggests that modulation of NMDA-Rs in CHR-participants may represent a viable strategy for novel treatment approaches. Administration of D-Serine, a NMDA-R agonist, significantly improved negative symptoms in a small sample of participants meeting CHR-criteria. Related evidence from the same investigators has shown that D-Serine also improves MMN-generation in chronic ScZ-patients (Kantrowitz, et al., 2016).

Another therapeutic target are impairments in oxidative stress that have been identified as a common factor in several animal models of ScZ and contribute to PV+ interneuron deficits and NMDA-R hypofunctioning (Steullet, et al., 2017). Administration of the antioxidant N-acetyl cysteine (NAC) in established ScZ has been shown to improve MMN-deficts as well as negative symptoms Do (Lavoie, et al., 2008). Related to the possibility of using NAC for the treatment of prodromal ScZ, Cabungcal et al. (2014) examined NAC to target the emergence of cognitive deficits in the neonatal ventral hippocampal lesion (NVHL) rodent model of ScZ. Administration of NAC in adolescent rats prevented the reduction of PV+ interneuron deficits in the PFC as well as electrophysiological and behavioral deficits observed in ScZ-patients, highlighting the potential of preventive treatments that target E/I-balance .for correction circuit abnormalities prior to the onset of ScZ.

Brain stimulation may represent an additional, emerging approach that could be harnessed in

the future to correct abnormalities in neural dynamics. Specifically, it is conceivable that aberrant oscillatory activity is targeted to with brain stimulation techniques, such as tACS and TMS, as evidence suggests that brain networks can be entrained at specific frequencies (Thut, Schyns, & Gross, 2011) This approach has been tested in in-vitro and in-vivo animal research as well as in human studies, all pointing towards converging evidence for the effectivity of the approach (Frohlich & McCormick, 2010; Ozen, et al., 2010)(Helfrich, et al., 2014).

Summary and Outlook

The current data provide preliminary support for the hypothesis that the prodrome of ScZ is associated with aberrant neuronal dynamics. Because of the possibility to link these parameters to basic circuit mechanisms, we believe that it is important to carry out further studies using advanced EEG/MEG-approaches that fully exploit advances in signal processing and source-reconstruction techniques to capture alterations in the spectral signatures and organization of large-scale networks. Together with systematic links with translational research, we believe that this approach could potentially lead to paradigm-changing approach in ScZ towards early intervention and treatment.

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Figure Legends

Figure 1: Model of psychosis onset from the clinical high-risk state. Self-experienced perceptual and cognitive abnormalities are considered to be earliest sign-posts for psychosis risk prior to the development of sub-threshold psychosis symptoms. (adapted from Fusar-Poli et al., 2013).

Figure 2: MMN-Findings in ScZ and Clinical High Risk Groups: a) Mean effect size and 95% confidence interval by group for MMN-deficits in ScZ, Bipolar, CHR- and first-degree relatives. CI, confidence interval; SZ, schizophrenia. (adapted from Erickson et al., 2015).
b) Duration MMN in CHR-participants. The solid black line represents the duration MMN in healthy controls, the solid gray line depicts the duration MMN in FEP-patients. HC, healthy control subjects; AR, at-risk subjects; FES, first-episode schizophrenia.
c) Relationship between MMN-deficits and transition to psychosis. Hazard function of the two risk classes generated by a median split. Cumulative hazard rate in Class 1 (dotted line) is .34 and .85 in Class 2 (solid line). Follow-up periods exceeding 24 months were considered at the end of Month 24. (adapted from Bodatsch et al., 2011).

Figure 3: ASSR-Findings in ScZ and Clinical High Risk Groups: a) Meta-Analysis of 40 Hz

ASSR in ScZ. Hedges *g* random-effect sizes for 20 studies, showing power and phase effects separately. Across studies, the Hedges *g* random-effect size was −0.46 for phase measures and −0.58 for power measures. For both measures combined, the overall effect size was −0.50.

b) EEG 40 Hz ASSR-data in CHR-participants. Left panel: Figure 2. Time course of the 40-Hz ITC. The x-axis indicates time (ms), and the y-axis indicates ITC. The blue line, dotted line, and purple line indicate the 40-Hz ITC in healthy controls, ultra-high risk, and FEP schizophrenia, respectively. Right Panel: The time course of the 40-Hz ERSP. The x-axis indicates time (ms), and the y-axis indicates ERSP. The blue line, dotted line, and purple line indicate the 40-Hz ERSP in healthy controls, ultra-high risk, and first-episode schizophrenia, respectively. (adapted from Tada et al., 2016).

c) 40 Hz ASSR and NMDA-R modulation: Heat map representation of mean PLF measure at the 7 min point following vehicle (a) or ketamine [1 (b) or 30 (c) mg/kg] treatments. Dashed boxes indicate computed activity within the gamma band (35–45 Hz) for the duration of the stimulus train (0.5 s). In comparison to the vehicle group, note a clear increase after 1 mg/kg ketamine treatment and a reduction after 30 mg/kg treatment. Statistical significance indicated by *Po0.05; Dunnett's test. (adapted from Sivarao et al., 2016)

Figure 4. MRS Glutamate Findings in ScZ and Clinical High Risk Groups

a) Overview of MRS Glutamate findings in ScZ. Negative Hedges *g* values denote lower glutamatergic metabolite concentrations in cases than controls; positive values denote higher glutamatergic metabolite concentrations in cases than controls. The size of the data markers is proportional to the total number of individuals. DLPFC indicates dorsolateral prefrontal

cortex; Glx, combined glutamate and glutamine signal; MTL, medial temporal lobe; and WM, white matter. (adapted from Merritt et al., 2016).

b) MRS Glutamate findings in CHR-participants. Location of voxel placement for MRS acquisition and glutamate levels in the region of interests: left hippocampus (upper left), anterior cingulate (upper right), right thalamus (lower left). Error bars show the 95% confidence intervals of the means. ARMS indicates at-risk mental state. (adapted from (P. Fusar-Poli 2011).

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