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Functional cognitive and cortical abnormalities in chronic and first-admission schizophrenia

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ABSTRACT

Evoked and induced event-related neural oscillations have recently been proposed as a key mechanism supporting higher-order cognition. Cognitive decay and abnormal electromagnetic sensory gating reliably distinguish schizophrenia (SZ) patients and healthy individuals, demonstrated in chronic (CHR) and first-admission (FA) patients. Not yet determined is whether altered event-related modulation of oscillatory activity is manifested at early stages of SZ, thus reflects and perhaps embodies the development of psychopathology, and provides a mechanism for the gating deficit. The present study compared behavioral and functional brain measures in CHR and FA samples. Cognitive test performance (MATRICS Consortium Cognitive Battery, MCCB), neuromagnetic event-related fields (M50 gating ratio), and oscillatory dynamics (evoked and induced modulation of 8–12 Hz alpha) during a paired-click task were assessed in 35 CHR and 31 FA patients meeting the criteria for ICD-10 diagnoses of schizophrenia as well as 28 healthy comparison subjects (HC). Both patient groups displayed poorer cognitive performance, higher M50 ratio (poorer sensory gating), and less induced modulation of alpha activity than did HC. Induced alpha power decrease in bilateral posterior regions varied with M50 ratio in HC but not SZ, whereas orbitofrontal alpha power decrease was related to M50 ratio in SZ but not HC. Results suggest disruption of oscillatory dynamics at early stages of illness, which may contribute to deficient information sampling, memory updating, and higher cognitive functioning.

1. Introduction

Cognitive deficits have been reported in first-admission[1] patients with schizophrenia (e.g., Heinrichs, 2004; Mesholam-Gately et al., 2009; Wobrock et al., 2009; Bechard-Evans et al., 2010; Fromman et al., 2011), with few specific functions distinguishing chronic (CHR) and first-admission (FA) samples (Hilti et al., 2010; Holmén et al., 2010; Kelleher et al., 2013). Whereas cognitive performance measures have the virtue of likely being relatively close to the clinical symptoms that define schizophrenia, structural and functional brain measures are believed to be closer to the genetic contributors. Given that the causal story in schizophrenia is likely to be complex (Kendler, 2005; Miller, 2010), interest is growing in psychological and biological endophenotypes, which are expected to reveal intermediate mechanisms in mental illness (Gottesman and Gould, 2003; Miller and Rockstroh, 2013). Findings of gray-matter loss (Salisbury et al., 2007; deLisi, 2008; Sun et al., 2009a,b; Asami et al., 2012) as well as disrupted white-matter integrity (Liu et al., 2013) starting early and progressing with course of illness suggest early pathophysiology. Among the brain measures evaluated as most robustly distinguishing schizophrenic and healthy individuals, P50 sensory gating[2] has been found to produce even larger effect sizes than cognitive performance measures (Heinrichs, 2004). Abnormal sensory gating has been

Abbreviations: SZ, schizophrenia; FA, first admission; CHR, chronic; HC, healthy comparison subjects.

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[1] Articles refer to early-onset, first-episode, or first-admission patients, but most such samples are young adults, recruited shortly after their first hospitalization, undergoing treatment for a schizophrenia spectrum disorder. The term 'first-admission' is used here to represent such early phases and because the present sample is in fact first-admission.

[2] Sensory gating refers to a phenomenon of cortical response suppression to the second of two identical stimuli presented in rapid succession. This attenuation is thought to reflect a brain mechanism inhibiting the processing of redundant information, thus protecting the processing of information already under analysis. Both stimuli typically evoke an electromagnetic response ~50 ms after stimulus onset, P50. The S2-evoked P50/S1-evoked P50 amplitude ratio commonly serves as a measure of sensory gating. M50 is the MEG analog of the EEG P50.

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reported early in the development of schizophrenia (Brockhaus-Dumke et al., 2008; Keri et al., 2010; Yee et al., 2010), though less consistently than cognitive deficits (e.g., deWilde et al., 2007; Bachmann et al., 2010).

Electromagnetic oscillatory dynamics, proposed as indicating information flow within and across neural networks (e.g., Jensen and Mazaheri, 2010; Buzsaki and Watson, 2012), may be promising endophenotypes for mental illness (e.g., Uhlhaas et al., 2008; Uhlhaas and Singer, 2010; Uhlhaas, 2011; Uhlhaas and Singer, 2012; Buzsaki et al., 2013). Reduced evoked and induced activity in schizophrenia patients has been reported in higher (60–80 Hz, gamma) and lower (4–7 Hz, theta) frequency bands (Uhlhaas et al., 2008; Woo et al., 2010). Evidence of oscillatory abnormalities in schizophrenia has been largely confined to CHR samples. The few studies involving FA patients indicate similar abnormalities in theta (e.g., Missonnier et al., 2012) and gamma activities (e.g., Symond et al., 2005; Haenschel et al., 2009; Minzenberg et al., 2010). Analyzing event-related (M50 gating ratio) and oscillatory measures in the paired-click design, Popov et al. (2011) reported a sequence of S1-evoked gamma power increase and induced alpha power decrease around S2, which was proposed as a mechanism enabling efficient auditory gating. Smaller evoked and induced alpha power modulation in CHR and a relationship of abnormally high gating ratio with smaller alpha power modulation (see also Hall et al., 2011; Hamm et al., 2012) were interpreted as an evidence of less efficient engagement of relevant neural networks supporting initial stimulus encoding, sustained attention, and comparison with stored memory traces.

To evaluate the hypothesis that the abnormalities reported in Popov et al. (2011) in CHR manifested early in the illness, the present study compared cognitive test performance and neuromagnetic activity in CHR and FA samples. The first two specific predictions were framed to reject that hypothesis. (1) CHR will perform worse than FA on standard cognitive tests, perhaps reflecting chronicity and/or long-term neuroleptic treatment rather than abnormal processing fundamental to schizophrenic psychopathology. (2) CHR will show high M50 ratios (poor gating) and abnormal oscillatory dynamics, whereas FA will show M50 ratios and oscillatory dynamics similar to those of HC. (3) M50 ratios and oscillatory dynamics will correlate, providing evidence that oscillatory dynamics reflect fundamental aspects of neural information processing that contribute to cognition.

2. Methods and materials

2.1. Participants

Sixty-six inpatients were diagnosed by experienced senior psychiatrists or psychologists using ICD-10 criteria and recruited from the CHR and FA inpatient units of the regional Center for Psychiatry. Based on hospitalization records, 35 CHR had 3 to 20 inpatient admissions,[3] and 31 FA were diagnosed and hospitalized for the first time. ICD 10 Diagnoses for CHR were $n = 30$ with paranoid-hallucinatory schizophrenia (F20.0); $n = 4$ with schizoaffective disorder (F25.1); $n = 1$ with psychotic episode (F23.2). The FA group consisted of $n = 24$ with F20.0, $n = 3$ with F25.1, $n = 2$ with F23.1, and $n = 2$ with F23.2. First experiences of positive symptoms in FA were reported to be on average of 8.7 weeks (range 1–52) before admission. The samples did not overlap with those of Popov et al. (2011).

Inclusion criteria for patients were normal intellectual function and no history of neurological condition or disorder, including epilepsy or head trauma with loss of consciousness. At the time of the laboratory assessment, clinical status was characterized by Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) symptom score and Global Assessment of Functioning (GAF, DSM-IV Axis V). Patient groups (Table 1) did not differ in gender distribution, IQ (assessed by a standard German test for premorbid intelligence, MWT-B; Lehrl, 2005), years of education, or symptom scores. As expected, FA patients were younger than CHR patients. None of the FA patients had been treated with neuroleptics before admission, but all had started neuroleptic medication by the time of the assessment. CHR and FA patients did not differ in current chlorpromazine equivalent (CPZ).

Twenty-eight healthy comparison subjects (HC) were recruited to be demographically comparable to the SZ sample. HC were screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) to exclude psychiatric or neurological disorder. HC did not differ from SZ in gender distribution or age (Table 1). HC had 1.6 more years of education than SZ.

Participants provided written informed consent prior to the study, which comprised two sessions (cognitive testing and MEG paired-click task). They received 30 Euro upon completion. The study was approved by the ethics committee of the University of Konstanz.

2.2. Material and methods

2.2.1. Cognitive performance assessment and analysis

The MATRICS Consortium Cognitive Battery (MCCB, Nuechterlein and Green, 2006) was used for the assessment of cognitive performance. The MCCB covers domains of cognitive functions that have been shown to be impaired in schizophrenia, including processing speed, attentional vigilance, working memory, verbal learning, visual learning, reasoning, and social cognition. Raw scores were converted to T-scores based on a USA representative community sample of healthy subjects (Nuechterlein and Green, 2006; German norms have not been developed). Normal distribution was verified by the Kolmogorov–Smirnov test. Group differences in the mean T-scores for each domain and for an overall composite score were evaluated by ANOVAs using two a priori orthogonal between-subject contrasts: comparing SZ and HC (MCCB data available for 25 of the 28 HC) and comparing the two patient samples. These were used in a Group × Domain analysis, with the within-subject factor Domain comparing the seven cognitive domains using Huynh–Feldt epsilon correction. The comparison of SZ and HC served to replicate reported abnormalities in schizophrenia. The comparison of CHR and FA addressed the main hypothesis about abnormalities that manifest early in the course of disease. Significant main effects and interactions were followed up with appropriate comparisons.

2.2.2. Neural activity assessment and analysis

2.2.2.1. Paired-click design. Prior to MEG measurement, individual hearing levels were determined for each ear separately via an adapted method of limits (Gescheide, 1997). The paired-click procedure comprised 100 pairs of 3 ms square-wave clicks (S1 and S2) presented with a 500 ms onset-to-onset interstimulus interval and a variable offset to onset interval of 7 to 9 s. Clicks were presented 60 dB above individual hearing level and delivered via 5 m nonferromagnetic tubes. No performance task was involved, except that participants were asked to keep their eyes focused on a small fixation point throughout the procedure.

2.2.2.2. Neuromagnetic data acquisition and analyses. Details of MEG data collection and analysis were described in Popov et al. (2011) and in In the supplement: method details. For artifact-free trials (on average 95 trials/participant with no group differences: CHR 95.3 ± 5.5; FA 93.6 ± 9.8; HC 95.5 ± 5.3; $F < 1$), epochs of 1000 ms before and 2000 ms following the first click (S1) were extracted from continuous recordings. M50 was scored from epochs extending 100 ms before and 400 ms after each click (S1 and S2). Neural sources were estimated by fitting a pair of regional sources simultaneously in the left and right hemispheres

[3] For three patients the precise number of admissions could not be verified from files because some of the prior admissions were at hospitals for which records were not available. For these patients, careful diagnostic interviews confirmed illness duration >3 years together with a minimum of 3 inpatient and/or outpatient treatment occasions.

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