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Prolonged cortical silent period among drug-naive subjects at ultra-high risk of psychosis

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ABSTRACT

Background: Deficits in gamma-aminobutyric acid (GABA) inhibitory neurotransmission have been associated with pathophysiological mechanisms underlying schizophrenia. However, little is known about whether these deficits occur before or after the onset of psychosis.
Method: We recruited 16 drug-naive subjects at ultra-high risk of psychosis (UHR), 17 schizophrenia patients and 28 healthy controls. Cortical inhibition was determined using transcranial magnetic stimulation (TMS) over the left primary motor cortex. TMS markers such as short-interval cortical inhibition (SICI), cortical silent period (CSP) and intracortical facilitation (ICF) were obtained from each subject. While SICI can reflect GABA type A ($GABA_A$) mediated inhibition, CSP is thought to indicate GABA type B ($GABA_B$) mediated inhibitory circuits.
Results: As compared with healthy controls, UHR subjects showed a prolonged CSP with no change in SICI, whereas schizophrenia patients demonstrated both a prolonged CSP and a reduced SICI. No group differences were found for ICF. CSP in schizophrenia patients also had a positive correlation with positive symptom score of the positive and negative symptom scale (PANSS).
Conclusions: Cortical inhibitory deficits among UHR subjects were relatively limited compared to those among schizophrenia patients. Alterations might occur in some subgroup of GABA-mediated neurotransmitter systems before the onset of psychosis, while alterations in both $GABA_A$ and $GABA_B$ networks might contribute to full-blown psychosis.

1. Introduction

Schizophrenia (SZ) is a severe and lifelong psychotic disorder involving perceptual, behavioral and cognitive impairments (Daskalakis et al., 2007). Recent investigations place an emphasis on the "ultra-high risk (UHR)" phase or "prodrome" to psychosis, the period of imminent risk for developing psychosis in adolescents and young adults (Fusar-Poli et al., 2013). During this period, UHR subjects experience some mild or attenuated psychotic symptoms and cognitive disturbances, and seek help from doctors (Zhang et al., 2013). Diagnostic instruments such as Comprehensive Assessment of At Risk Mental States (CAARMS) or Structured Interview for Prodromal Syndromes (SIPS) are developed to identify a subject's level of risk (Miller et al., 2003; Yung et al., 2005). UHR subjects are reported to convert into diagnosable psychosis with an average rate of 20% after one year and about 35% over 3 years (Cannon et al., 2008; Fusar-Poli et al., 2012). This progression tends to be accompanied by illness-related deterioration of both subjects' brain structures as well as their cognitive/social functions (Woods et al., 2010). Findings from UHR subjects will certainly shed light on our understanding of the pathophysiological mechanisms of schizophrenia, reduce the duration of untreated psychosis and result in better outcome of treatments (Fusar-Poli et al., 2013).

Dysfunctional gamma-aminobutyric acid (GABA) inhibitory neurotransmission has been linked extensively to the pathophysiology of schizophrenia for a long time (Gonzalez-Burgos and Lewis, 2008). Both GABAergic interneurons and an important precursor for GABA synthesis, the 67-kDa isoform of glutamic acid decarboxylase (GAD67), have been found to lessen in schizophrenia patients' brains (Benes, 1998; Lewis et al., 2005). Additionally, neurophysiological studies

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have provided more evidence for the role of GABA in schizophrenia from sensory gating of auditory P50 potential and gamma band oscillations (Oranje and Glenthøj, 2013). Reduced auditory P50 suppression reflects impaired inhibitory gating of the brain's response to repeated auditory stimuli in schizophrenia patients (Chen et al., 2011; Oranje and Glenthøj, 2013). Abnormal gamma synchrony of schizophrenia, another manifestation of impaired GABAergic inhibitory neurotransmission, has been related to the severity of psychotic symptoms (Spencer et al., 2003; Spencer et al., 2004). In vivo measurements of GABA levels using proton magnetic resonance spectroscopy (^{1}H-MRS) have reported increased medial frontal GABA in unmediated schizophrenia patients (Kegeles et al., 2012), whereas lower GABA/Cr ratios have been found in basal ganglia in early-stage schizophrenia patients (Goto et al., 2009; Rowland et al., 2013). Both direct and indirect evidence for GABA alterations in schizophrenia demonstrates that GABA inhibitory neurotransmission is likely to play a key role in the occurrence and development of psychosis (Radhu et al., 2013; Rogasch et al., 2013; Rowland et al., 2013).

Recently, non-invasive transcranial magnetic stimulations (TMS) has provided a more safe and convenient method to measure the cortical inhibitory deficits which reflect disturbed GABAergic circuits in schizophrenia patients (Farzan et al., 2012). Various TMS markers have been developed, including short-interval cortical inhibition (SICI), cortical silent period (CSP) and intra-cortical facilitation (ICF), and have been linked to different subtypes of GABA receptors (Hasan et al., 2013). Specifically, SICI is most likely associated with GABA type A ($GABA_A$)-mediated inhibition (Ziemann et al., 1996b), while CSP may reflect GABA type B ($GABA_B$)-mediated inhibitory intracortical networks (Roick et al., 1993; Siebner et al., 1998). Pharmacological studies in humans have demonstrated that blockade of $GABA_B$ uptake with tiagabine (TGB) or baclofens leads to a dose-dependent prolongation of CSP (Siebner et al., 1998; Werhahn et al., 1999). Administrations of lorazepam which facilitates $GABA_A$ neurotransmission produce a significant increase in SICI (Ziemann et al., 1996a; Di Lazzaro et al., 2005). Furthermore, the time courses of CSP and SICI are similar to $GABA_B$ and $GABA_A$-mediated inhibitory postsynaptic potentials (IPSPs) by using intracellular recording in human and rat (Deisz, 1999; Radhu et al., 2012; Radhu et al., 2013). ICF is most likely glutamate-mediated by excitatory neuronal circuits (Ziemann, 2004; Hasan et al., 2013) (Fig. 1).

Where previous studies have consistently found a reduced SICI in schizophrenia, suggesting impaired $GABA_A$-mediated inhibition (Radhu et al., 2013), results pertaining to CSP in schizophrenia patients are more controversial. One noticeable trend has seen a prolonged CSP among both first episode patients and clozapine medicated chronic patients compared with healthy controls, suggesting alterations within the $GABA_B$-mediated neurotransmitter system in schizophrenia (Daskalakis et al., 2002; Liu et al., 2009; Soubasi et al., 2010; Ochoa et al., 2012). However, one study found no significant differences in CSP between SZ patients and healthy controls (Puri et al., 1996), and others have reported a shortened CSP in either the chronic or unmediated patients (Fitzgerald et al., 2002; Liu et al., 2009). Inconsistent CSP results have been explained by differences in clinical stages, the severity of psychotic symptoms and medication treatments (Carletti et al., 2012; Radhu et al., 2013; Rogasch et al., 2013). Most studies failed to find significant IFC differences between schizophrenia patients and healthy controls (Fitzgerald et al., 2002; Wobrock et al., 2008; Liu et al., 2009), possibly due to that ICF is mediated by a distinct intra-cortical network from SICI or CSP (Fitzgerald et al., 2002). Based on these findings, it has been suggested that both $GABA_A$ and $GABA_B$ mediated inhibition are affected in schizophrenia (Hasan et al., 2013).

To rule out the influences of confounding factors such as medication treatments, in vivo measurements of cortical inhibition among drug-naive UHR subjects can help to address whether deficits in GABA mediated cortical inhibition occur before or after full-blown psychosis for schizophrenia. To the best of our knowledge, only Hasan et al. have investigated cortical inhibition among UHR subjects (Hasan et al., 2012). They reported only a reduced SICI and no significant change of CSP in UHR subjects, but both reduced SICI and prolonged CSP in first-episode schizophrenia patients (Hasan et al., 2012). These findings made them postulate that $GABA_A$ dysfunctions possibly occur early in the time course of the disease, whereas alterations in the $GABA_B$ mediated network seem to occur later in the disease's progression (Hasan et al., 2012). UHR subjects in that study were antipsychotic naive, but about half of them were medicated with an antidepressant or zopiclone when participating in the study. A few studies have reported that antidepressants may affect GABA-mediated cortical inhibition (Luparini et al., 2004; Choi et al., 2010; Radhu et al., 2012). Additionally, one study found only lacked transcallosal inhibition rather than that of other TMS parameters in first-degree relatives of schizophrenia patients, who show psychosis-proneness but are free of confounds related to medication and/or florid psychosis (Saka et al., 2005; Nagai et al., 2013). Therefore, it is necessary to replicate the alterations in cortical inhibition among UHR subjects who are both antipsychotic-naive and antidepressant-naive.

The aim of the present study is to investigate cortical inhibition measured by TMS markers among UHR subjects who are both antipsychotic-naive and antidepressant-naive on their first visit to our hospital. By comparing these markers with schizophrenia patients and healthy controls, we hypothesized that GABA mediated inhibition was limited and partially affected before full-blown psychosis. Therefore,

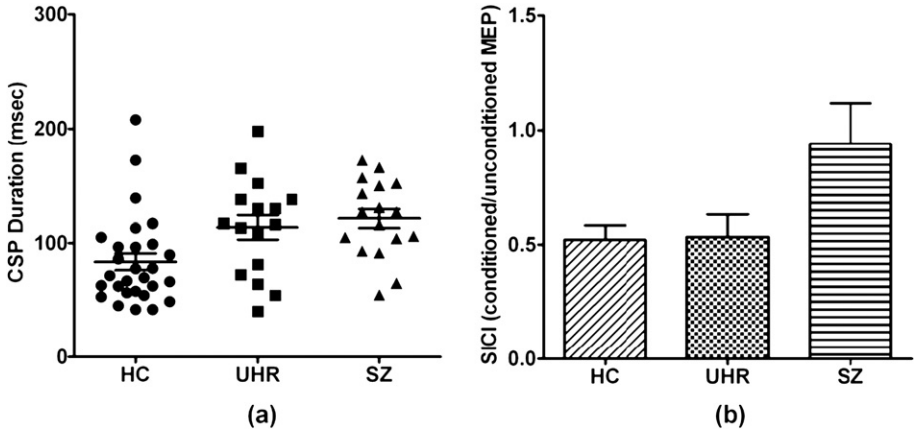

Fig. 1. Cortical silent period (CSP) and short interval cortical inhibition (SICI) in subjects at ultra-high risk of psychosis (UHR), schizophrenia patients (SZ) and healthy controls (HC). (a) There was a significant group effect on CSP. Post-hoc tests showed a longer CSP in both SZ and UHR groups than in HC. (b) The group effect on SICI approached a significant level. Exploratory test revealed that an attenuated SICI only in SZ group but not in UHR group, as compared to HC group.