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

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A R T I C L E  I N F O

Article history:
Received 11 July 2014
Received in revised form 9 September 2014
Accepted 7 October 2014
Available online 31 October 2014

Keywords:
Ultra-high risk of psychosis
Schizophrenia
Cortical inhibition
Short-interval cortical inhibition
Cortical silent period

A B S T R A C T

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.

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1. Introduction

Schizophrenia (SZ) is a severe and lifelong psychiatric 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 isofrom of glutamic acid decarboxylase (GAD67), have been found to lessen in schizophrenia patients’ brains (Benes, 1998; Lewis et al., 2005). Additionally, neurophysiological studies...
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 (1H-MRS) have reported increased medial frontal GABA in unmedicated 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 inhibition 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) have 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_A uptake with tiagabine (TGB) or baclofen leads to a dose-dependent prolongation of CSP (Siebner et al., 1998; Werhahn et al., 1999). Administrations of lorazepam which facilitates GABA_B 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_A and GABA_B-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_A-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 unmedicated 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,

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**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.
inhibitory deficits would appear in UHR subjects, but not as severe as those present in schizophrenia patients.

2. Method

2.1. Subjects

2.1.1. UHR group

Sixteen individuals meeting the criteria for at-risk mental state, as defined by the Structured Interview for Prodromal Syndromes (SIPS) and Scale of Prodromal Syndromes (SOPS), were recruited from Shanghai Mental Health Center (SMHC) (Miller et al., 2003; Zhang et al., 2013). All UHR subjects met the criteria of Attenuated Positive Syndrome (APSS). SIPS interviews were conducted by a senior psychiatrist (T. Zhang) who was certified on the SIPS at Yale University sponsored SIPS/SOPS trainings (Zhang et al., 2013). The majority of UHR subjects got a rating of 3 or higher on subscales P1 (unusual thought content/delusional ideas), P2 (suspiciousness/persecutory ideas) and P4 (perceptual abnormalities/hallucinations) for positive symptoms in SOPS as shown in Table 1. The methods for identifying the characterizing symptoms with prodromal symptoms have been introduced in details elsewhere (Zhang et al., 2013). These UHR subjects were psychological clients and visited our hospital for seeking help for the first time when being recruited. Their prodromal symptoms had already lasted for 3.88 ± 2.84 months. Only subjects who had no history of being medicated were included in the present study. Their first visit. Therefore, all of our UHR subjects were drug-naive when being tested. However, eight UHR subjects were prescribed antipsychotic medications (risperidone 1–4 mg/day for 3, aripiprazole 5–10 mg/day for 2, olanzapine 5 mg/day for 1, quetiapine 100 mg/day for 1 and amisulpride 200 mg/day for 1) after the first clinical visit in our hospital. Follow-up of these UHR subjects is still ongoing.

2.1.2. Schizophrenia (SZ) group

Seventeen inpatients with schizophrenia were also recruited from SMHC. All patients met ICD-10 (the tenth revision of International Classification of Diseases) diagnostic criteria for schizophrenia. The majority of SZ subjects got a rating of 3 or higher on subscales P1 (delusional ideas), P3 (perceptual abnormalities/hallucinations) and P6 (suspiciousness/persecutory ideas) for positive symptoms in Positive and Negative Symptom Scale (PANSS) as also shown in Table 1 (Kay et al., 1987; Kay et al., 1988, 1989). All SZ patients had received antipsychotic medications. The mean daily dose for antipsychotic medications was converted to chlorpromazine (CPZ) equivalents (Patel et al., 2013). Fourteen patients were receiving treatment with one antipsychotic medication at a dose of 267.18 ± 109.51 mg/day in terms of CPZ. Three patients were receiving two antipsychotic medications at a dose of 362.33 ± 175.73 mg/day in terms of CPZ.

2.1.3. Healthy controls (HC)

Twenty-eight healthy controls were recruited by advertisements. All subjects completed the structural clinical interview by a research psychiatrist (T. Zhang) using The Mini-International Neuropsychiatric Interview (MINI) plus v 5.0 (Sheehan et al., 1998). All HC subjects had no history of mental retardation, neurological illness, severe physical disease, or substance/alcohol abuse.

The study was approved by the Research Ethics Committee at SMHC and written informed consent was obtained from each subject. Handedness was determined by self-report from each participant, and all subjects were right-handed (see Table 2). Global Assessment of Functioning (GAF) was assessed in the UHR group. In the SZ group, clinical symptoms were assessed using PANSS (Kay et al., 1987; Kay et al., 1988, 1989). None of the participants had any contraindication for TMS.

2.2. TMS procedure

All subjects were seated in a comfortable chair while TMS stimuli were delivered to the left primary motor cortex using a figure-of-eight coil and a MagPro X100 magnetic stimulator (Medtronic Co., Denmark). Electromyographic (EMG) signals were recorded from the right abductor pollicis brevis (APB) muscle with surface electrodes since all subjects were right-handed. EMG signals were amplified by Keypoint (Medtronic Co., Denmark) with a bandpass filter between 2 Hz and 10 kHz and then analyzed off-line. In each subject, the optimal position of the coil was defined as the stimulation site where the motor evoked potential (MEP) was the largest. This position was then marked on the scalp with iodine to identify the placement of the center of coil for all future measurements. The coil was held tangentially to the head, pointing backwards and about 45° lateral to the midline.

The resting motor threshold (RMT) was defined as the lowest intensity producing an MEP of 50 μV, peak-to-peak, in five out of ten trials in relaxed APB (Daskalakis et al., 2008). The cortical silent period (CSP) duration was measured in 20% tonically active APB by stimulating the motor cortex with an intensity of 120% RMT (Radhu et al., 2012). Calculations of CSP were determined from MEP onset to the recovery of any voluntary EMG activity. Ten trials were repeated to obtain the average CSP duration for each subject.

SICI and ICF were obtained according to previously published protocols using paired-pulse TMS stimuli (Wobrock et al., 2008). The first pulse was a subthreshold conditioning stimulus at an intensity of 80% RMT and the second was a suprathreshold testing stimulus at an intensity which could produce an average MEP of 1 mV in five out of ten trials. SICI and ICF were calculated using the ratio of the conditioned MEP amplitude to the unconditioned MEP amplitude. The interval between conditioning and the testing stimulus was set at 3 ms for the SICI paradigm, and at 10 ms for the ICF paradigm. Ten trials were repeated for each paradigm (Wobrock et al., 2008).

2.3. Statistical analyses

The assumption of normality was examined using Kolmogorov–Smirnov tests for distribution of all independent variables, including age and TMS parameters (SICI, SIC, and ICF) before performing data analysis. The group effect on CSP was measured using a one-way ANOVA due to its normal distribution. Post-hoc subgroup comparisons were performed using Fisher’s LSD for the variable CSP. The group effects on SICI and ICF were analyzed using Kruskal–Wallis test because the assumptions of normality of SICI and ICF were violated. Post-hoc subgroup comparisons were performed using Mann–Whitney U tests for SICI and ICF. Chi²-tests were performed to assess the group effect in the distributions of gender and handedness.

Spearman’s rank tests were performed between TMS parameters and age. Spearman’s rank tests were also used for determining correlations between TMS parameters and psychotic symptoms of SZ patients (PANSS), and correlations between TMS parameters and clinical symptoms of UHR subjects (SOPS).

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Table 1

<table>
<thead>
<tr>
<th>Positive symptoms</th>
<th>UHR (n = 16)</th>
<th>Percentage (%)</th>
<th>SZ (n = 17)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual thought content/delusional ideas</td>
<td>10</td>
<td>62.5</td>
<td>8</td>
<td>47.1</td>
</tr>
<tr>
<td>Suspiciousness/persecutory ideas</td>
<td>11</td>
<td>68.8</td>
<td>14</td>
<td>82.3</td>
</tr>
<tr>
<td>Perceptual abnormalities/hallucinations</td>
<td>10</td>
<td>62.5</td>
<td>10</td>
<td>58.8</td>
</tr>
</tbody>
</table>
3. Results

3.1. Demographic characteristics

There was no significant group effect on gender or handedness; however, there was a significant effect on age (F(2, 60) = 14.09, P < 0.01). Post-hoc tests showed the age of UHR group that was comparable to healthy controls (P = 1.00), but much younger than that of SZ patients (P < 0.01). Spearman’s rank tests revealed no significant correlation between age and TMS parameters in any group.

3.2. Motor threshold (MT)

The mean MT was 40.71% ± 4.29% for UHR group, 39.82% ± 4.59% for SZ group and 38.68% ± 5.46% for healthy controls. There was no significant difference in MT across three groups (F(2, 60) = 0.84, P = 0.44). Regarding MEP, the 1 mV-MEPs’ sizes did differ across groups (F(2, 60) = 3.57, P < 0.05). The MEP was smaller among schizophrenia patients (0.81 ± 0.23 mV) than among healthy controls (1.13 ± 0.46 mV, P < 0.05) and tended to be smaller than among UHR subjects (1.06 ± 0.37 mV, P = 0.07).

3.3. Short interval cortical inhibition (SICI)

The group effect on SICI was significant across three groups (χ²(2,60) = 7.11, P < 0.05). We further explored the group effects between SZ and HC groups and between UHR and HC groups using Mann–Whitney U tests, respectively. As shown in Fig. 2(b), SICI in SZ patients (0.94 ± 0.74) showed a reduced inhibition as compared to that in healthy controls (0.52 ± 0.34) (Z = −2.39, P < 0.05), whereas no difference in SICI was found between UHR subjects (0.53 ± 0.39) and healthy controls (Z = −0.27, P = 0.79). Additionally, the difference in SICI between SZ patients versus UHR subjects approached a significant level (Z = −2.27, P < 0.05).

3.4. Cortical silent period (CSP)

There was a significant effect of group on CSP (F(2, 60) = 6.01, P < 0.01) as depicted in Fig. 2(a). Post-hoc tests revealed that CSP was longer in both SZ patients (121.18 ± 33.87 ms) and UHR subjects (113.64 ± 42.43 ms) than in healthy controls (83.61 ± 38.96 ms) (SZ vs healthy controls, P < 0.01; UHR vs healthy controls, t = −2.38, P < 0.05). CSP did not differ between SZ and UHR groups (P = 0.58).

3.5. Intracortical facilitation (ICF)

The mean ICF was 1.57 ± 0.83 for healthy controls, 1.25 ± 0.63 for UHR subjects and 1.59 ± 0.85 for SZ patients. It did not differ among these three groups (χ²(2,60) = 1.90, P = 0.39).

3.6. Correlation of TMS parameters with clinical symptoms

Results of correlation coefficients of TMS parameters with psychotic symptoms of SZ patients and with symptoms of UHR are summarized in Table 3. Schizophrenia patients showed a positive correlation between PANSS positive symptom score and CSP duration (r = 0.49, P < 0.05), which

Table 2
Demographic and clinical characteristics of subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>UHR</th>
<th>SZ</th>
<th>HC</th>
<th>Group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size</td>
<td>16</td>
<td>17</td>
<td>28</td>
<td>–</td>
</tr>
<tr>
<td>Age: years (SD)</td>
<td>20.94 (6.63)</td>
<td>31.71 (9.00)</td>
<td>20.93 (6.02)</td>
<td>F(2, 60) = 14.09, P &lt; 0.001</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>9/7</td>
<td>9/8</td>
<td>15/13</td>
<td>–</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>16/0</td>
<td>17/0</td>
<td>28/0</td>
<td>–</td>
</tr>
<tr>
<td>SIPS—positive</td>
<td>9.19 (3.47)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SIPS—negative</td>
<td>13.31 (5.85)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SIPS—disorganization</td>
<td>6.44 (3.83)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SIPS—general</td>
<td>7.56 (2.66)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GAF (past/current)</td>
<td>81.00 (4.77)/54.63 (8.89)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PANSS total</td>
<td>–</td>
<td>68.47 (6.71)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>–</td>
<td>17.71 (4.24)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>–</td>
<td>18.71 (5.75)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PANSS general</td>
<td>–</td>
<td>32.06 (3.70)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Illness duration: years</td>
<td>–</td>
<td>7.58 (4.72)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dosage of medications (mg/day in CPZ)</td>
<td>–</td>
<td>283.97 (122.48)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

UHR: ultra-high risk of psychosis; SZ: schizophrenia; HC: healthy controls; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; CPZ: chlorpromazine.

Fig. 2. Correlations of TMS parameters with psychotic symptoms in SZ group. There was a positive correlation between PANSS positive symptom score and CSP duration (r = 0.49, P < 0.05) as shown in (a), and there was a negative correlation between PANSS negative symptom score and ICF (r = −0.52, P < 0.05) as shown in (b).
was also shown in Fig. 2(a). A longer CSP was associated with a higher score of positive symptoms in SZ patients. The correlation between PANS negative symptom score and ICF was also significant for SZ patients \( (r = -0.52, P < 0.05) \). As shown in Fig. 2(b), a higher negative symptom score was associated with a lower ICF among SZ patients as well. UHR subjects showed a negative correlation between SOPS positive symptom score and ICF \( (r = -0.58, P < 0.05) \). However, neither CSP nor SICI showed any significant correlation with SOPS scores among UHR subjects.

### 4. Discussion

This is the first study to examine cortical inhibition among UHR subjects who are both antipsychotic-naïve and antidepressant-naïve. The overall results of this study indicate that UHR subjects show a different profile of cortical inhibition from schizophrenia patients. While medicated SZ patients showed both a prolonged CSP and an attenuated SICI, UHR subjects only demonstrated the prolonged CSP with no significant change in SICI compared to healthy controls. Schizophrenia patients’ CSP also showed a positive correlation with their positive symptom score of PANS, ICF did not differ across three groups, though it did have an inverse correlation with the negative symptom score of PANS among SZ patients.

Our results of cortical inhibition from schizophrenia patients are consistent with those reported by previous studies (Hasan et al., 2013; Radhu et al., 2013; Rogers et al., 2013). SICI reduction was a consistent finding in schizophrenia, which is independent of medication treatments and illness stage. This result has been supported in both medicated and unmedicated patients, and in both first-episode and chronic patients (Daskalakis et al., 2002; Fitzgerald et al., 2002; Fitzgerald et al., 2007; Radhu et al., 2012; Zhang et al., 2013). The clozapine-induced presynaptic GABAB receptor which was prolonged in patients treated by clozapine, which was explained as a compensation for other primary deficits (Daskalakis et al., 2002; Liu et al., 2009). Future studies are needed to understand these controversial CSP changes in more details. Alterations in CSP, either increases or decreases, both likely reflect the deficits in GABAergic-mediated neurotransmission in schizophrenia (Carletti et al., 2012). By combining results from both SICI and CSP, it is possible that both GABAergic and GABAB-mediated cortical inhibitions are affected in schizophrenia.

Results from UHR subjects provided more evidence for cortical inhibitory deficits at the early stage of psychosis. Since our UHR subjects are both antipsychotic naïve and antidepressant naïve, the effect of medications can be excluded. The major finding was a prolonged CSP duration in UHR subjects, suggesting that a potentiation of GABAergic-mediated inhibition had occurred before the onset of psychosis. This result was similar to that seen in first episode schizophrenia (Rogasch et al., 2013). At the same time, our UHR subjects showed no significant change in SICI, suggesting a relatively intact GABAergic-mediated neurotransmission. This profile was similar to results among depressive patients in Levinson et al.’s study where they reported abnormal CSP in all patients including medicated individuals with treatment-resistant depression, medicated euthymic participants and unmedicated depressed patients) and a reduced SICI in only those patients with treatment-resistant depression (Levinson et al., 2010). They suggested that the depressed state may be linked to GABAergic deficits, however, severe symptomatology, as seen in medication-resistant depression, may be linked to deficits in both GABAergic and GABAergic neurotransmission. Hasan et al. reported a reduced SICI together with a normal CSP in their UHR subjects, supporting a selective deficit in GABAergic neurotransmission dependent on disease stage (Hasan et al., 2012). What Hasan et al.’s and our study, among UHR subjects, have in common is that the GABA neurotransmitter system was partially impaired (in either GABAergic or GABABergic) before the onset of psychosis.

The alterations of two GABA subgroups differed between UHR subjects and SZ patients, which could be discussed as the interplay between GABAergic-mediated and GABABergic-mediated neurotransmitter systems (Hasan et al., 2013; Wu and Sun, 2014). CSP is mediated by the metabotropic GABAergic receptor which is both presynaptic and postsynaptic, and SICI is mediated by the ionotropic GABAergic receptor which is primarily postsynaptic (Radhu et al., 2012; Rogers et al., 2013). Alterations of GABABergic-mediated CSP are likely to have an influence on GABAergic-mediated SICI. One study in the developing rat hypothalamus reported that activity at GABAergic receptors modulated the excitatory responses mediated by GABAergic receptors by depressing the intracellular Ca²⁺ increase (Wu and Sun, 2014). There was also evidence that CSP was prolonged in patients treated by clozapine, which was explained as a compensatory GABAergic-mediated enhancement (Daskalakis et al., 2007; Zhang et al., 2013). The clozapine-induced presynaptic GABAergic receptor activation may decrease GABA release and lead to a subsequent decrease in postsynaptic GABAergic receptor activation (Daskalakis et al., 2007; Zhang et al., 2013). When we reviewed the previous studies

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### Table 3

<table>
<thead>
<tr>
<th>RMT</th>
<th>1mV MEP</th>
<th>CSP</th>
<th>SICI</th>
<th>ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PANSS of SZ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>( r = -0.02, P = 0.94 )</td>
<td>( r = 0.23, P = 0.38 )</td>
<td>( r = 0.38, P = 0.14 )</td>
<td>( r = -0.01, P = 0.98 )</td>
</tr>
<tr>
<td>Positive</td>
<td>( r = -0.29, P = 0.25 )</td>
<td>( r = -0.62, P &lt; 0.01 )</td>
<td>( r = 0.49, P = 0.05 )</td>
<td>( r = -0.09, P = 0.74 )</td>
</tr>
<tr>
<td>Negative</td>
<td>( r = 0.21, P = 0.42 )</td>
<td>( r = 0.67, P &lt; 0.01 )</td>
<td>( r = -0.17, P = 0.51 )</td>
<td>( r = 0.04, P = 0.87 )</td>
</tr>
<tr>
<td>General</td>
<td>( r = -0.03, P = 0.91 )</td>
<td>( r = 0.08, P = 0.77 )</td>
<td>( r = 0.20, P = 0.44 )</td>
<td>( r = -0.24, P = 0.36 )</td>
</tr>
<tr>
<td><strong>SOPS of UHR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>( r = -0.41, P = 0.11 )</td>
<td>( r = -0.45, P = 0.08 )</td>
<td>( r = 0.20, P = 0.47 )</td>
<td>( r = -0.28, P = 0.29 )</td>
</tr>
<tr>
<td>Negative</td>
<td>( r = -0.24, P = 0.36 )</td>
<td>( r = -0.35, P = 0.19 )</td>
<td>( r = -0.12, P = 0.67 )</td>
<td>( r = -0.13, P = 0.64 )</td>
</tr>
<tr>
<td>Disorganized</td>
<td>( r = -0.16, P = 0.57 )</td>
<td>( r = -0.07, P = 0.80 )</td>
<td>( r = -0.12, P = 0.66 )</td>
<td>( r = -0.23, P = 0.40 )</td>
</tr>
<tr>
<td>General</td>
<td>( r = -0.08, P = 0.76 )</td>
<td>( r = 0.05, P = 0.84 )</td>
<td>( r = -0.36, P = 0.17 )</td>
<td>( r = -0.44, P = 0.09 )</td>
</tr>
</tbody>
</table>

RMT, resting motor threshold; MEP, motor evoked potential; CSP, cortical silent period; SICI, short interval cortical inhibition; ICF, intracortical facilitation. Significant correlations between TMS and clinical symptoms (\( P < 0.05 \)) are shown in italics.
which include both SICI and CSP durations, we found these two TMS markers were both altered in schizophrenia (Daskalakis et al., 2002; Fitzgerald et al., 2002; Fitzgerald et al., 2002; Choi et al., 2009; Liu et al., 2009). These findings suggested that, before the onset of a psychotic episode or during the prodromal phase, the cortical inhibitory deficits are possibly limited to one subgroup of GABA receptors, and modulated by the other subgroup. If cortical inhibitory deficits occur in both GABA$_A$ and GABA$_B$ receptors, they will result in full-blown psychosis.

At present, we could not rule out the effect of other neurotransmitter systems such as the dopaminergic system on TMS parameters. Dopamine D2 antagonists were involved in antipsychotic response (Daskalakis et al., 2007). Studies on their involvement in the alterations on the TMS measurements are limited with most evidence coming from healthy volunteers (Hasan et al., 2013). Intracortical inhibition was enhanced after receiving a single dose of dopamine receptor agonist (bromocriptine) and reduced by antagonists (haloperidol) (Ziemann et al., 1996b; Ziemann et al., 1997; Ziemann, 2004). A prolonged CSP was found after receiving a single dose of D2-related quetiapine while SICI was not affected (Langguth et al., 2008). However, whether the dopaminergic system directly alters these TMS parameters or indirectly affects them through GABAergic system still needs to be clarified.

Several factors could potentially explain the inconsistency between Hasan et al.’s and our studies. Firstly, the effects of antidepressants may have an influence on the TMS parameters that cannot be excluded in Hasan et al.’s study (Levinson et al., 2010; Hasan et al., 2012). Second, the composition of gender is slightly different between two studies. More males (n = 14) than females (n = 4) were included in their study whereas our study contained a more balanced distribution. In the present study, a longer CSP was found in females than in male UHR subjects (see supplementary Fig. S1) and using more males in Hasan et al.’s could have biased their results towards shorter CSP durations. Aside from the limited sample size, this preliminary finding suggests a possible effect of gender on CSP. Finally, two different TMS stimulators (a MagPro × 100 magnetic stimulator and a BiStim$^2$ magnetic stimulator) were used in Hasan et al.’s study and only one TMS stimulator was used in our study (a MagPro × 100). However, the sample size is small in both studies, suggesting either finding needs validation in a large sample of UHR populations and in longitudinal studies.

In addition, Spearman’s rank tests revealed no significant correlation between age and TMS parameters in any group even though SZ patients are older than UHR and HC subjects. A positive correlation between CSP durations and PANSS positive scores was found in patients with SZ. This is in line with the previous studies in which CSP durations were positively correlated with PANSS total scores and Global Assessment of Functioning scores (Ochoa et al., 2012). Patients with severe positive symptoms may have greater deficits in cortical inhibition such that compensatory GABA-mediated mechanisms were activated, producing longer CSP durations. In subjects with high risk of psychosis, no significant correlations between CSP durations and SOPS scores were observed, supporting the difference between psychotic and non-psychotic level of symptoms.

No difference in ICF was found across the three groups in the present study. Many previous studies also failed to find such a difference. We did find an inverse correlation of ICF with negative symptom score in schizophrenia patients, but its significance needs to be explored in future studies. The physiological significance of ICF is still not well known, but is thought to likely reflect glutamate-dependent intracortical neuronal circuits (Hasan et al., 2013). Other researchers suggest that ICF relies on a net balance between inhibition and excitability (Daskalakis et al., 2004).

In conclusion, 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 system before the onset of psychosis, while alterations in both GABA$_A$ and GABA$_B$ networks might contribute to full-blown psychosis.

Role of funding source

This work was supported by the National Natural Science Foundation of China (61102020, 61171032, 81171267, 8126120410, 81361120430), Shanghai Science and Technology Committee (15411960000), Shanghai Municipal Natural Science Foundation (12ZR1448400), National Key Clinical Disciplines at Shanghai Mental Health Center (OMA-MH, 2011-873) and Shanghai Key Laboratory of Psychotic Disorders (13dz2260500). Yingying Tang was supported by 2012 SjitU SMC-Morning Star Award for Young Investigator and 2013 SjitU School of Medicine Award for Excellent Young Faculty.

Contributors

YYT conceptualized the study, undertook the statistical analyses and wrote the first draft of the manuscript. THZ, BTZ, SSZ and CYL interviewed participants and collected their demographic and clinical characteristics. KZX, ZYQ, HL and QC collected the primary TMS data. HRC, YKZ, and LJJ managed the literature searches and statistical analyses. EB, CBL, DHV and JHV designed the study, provided supervision in the implementation of the study and edited the manuscript.

Conflict of interest

There are no conflicts of interest to report.

Acknowledgment

The authors wish to thank all the participants and clinicians for their corporation in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.10.004.

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Neuropsychopharmacol. Biol. Psychiatry 28 (7), 1117

Psychiatry 65 (6), 503–507.


