



Somatosensory timing deficits in schizophrenia

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ARTICLE INFO

Article history:

Received 5 June 2012

Received in revised form

11 November 2012

Accepted 14 November 2012

Keywords:

Steady state response (SSR)

Magnetoencephalography (MEG)

Somatosensory

Phase-locking

ABSTRACT

Schizophrenia is often accompanied by disturbances in motor behavior thought to result from abnormalities in the brain's timing mechanisms. Virtually all behavior has a motor component, and proper regulation of motor behavior is often dependent upon accurate registration of somatosensory input. This study uses the steady-state evoked response (SSR) to quantify the accuracy of timing of the neocortical response to rapidly presented tactile somatosensory stimuli in patients with schizophrenia compared to control subjects. We used magnetic evoked fields and source space projection to estimate the time course of equivalent current sources in somatosensory cortex. Wavelet-based time-frequency analysis was used to compute intertrial timing consistency and amplitudes. SSRs in schizophrenic subjects demonstrated decreased performance in both metrics to contralateral 25-Hz tactile stimulation. Previous studies have reported similar abnormalities in the SSR in both auditory and visual domains. The magnetic SSR to tactile stimuli is thought to reflect activation of layer 3 pyramidal cells in primary sensory cortex. Thus, these findings, as in other sensory domains, are suggestive of impaired GABAergic inhibitory interneuronal control of the timing of pyramidal cell activity. This deficit may be intrinsic to neocortex, or might reflect as well impairment of cerebellar and/or thalamic involvement. These findings reinforce the notion that abnormalities in the brain's timing mechanisms are a central component of the schizophrenia syndrome.

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1. Introduction

Motor control abnormalities are prominent in schizophrenia. These range widely and include unusual or poorly coordinated motor behaviors observed in home movies of very young children who later develop schizophrenia (Walker and Lewine, 1990), abnormal motor behaviors and control seen in patients prior to and after development of the disorder (Tarrant and Jones, 1999), abnormal motor function on neuropsychological testing (Hoff et al., 1996), abnormal neurological soft signs (Krebs et al., 2000; Chan and Gottesman, 2008), and abnormal generation and/or processing and interpretation of the corollary discharge (efference copy) accompanying motor acts – believed essential for separation of thoughts and actions generated by self from those of other persons (Feinberg, 1978; Ford and Mathalon, 2004; Ford et al., 2008). Accuracy of all such motor behaviors is dependent in part upon accuracy of somatosensory feedback. Central to such accuracy is timing. Beta-band oscillations in the somatosensory cortex, and this process is synchronized with those in motor cortex and this is thought to be a possible mechanism for the mediation of corticomuscular coherence (for review, see Baker, 2007).

Inaccurate or noisy somatosensory feedback will likely result in impaired generation, coordination, and interpretation of motor behavior. While numerous studies have demonstrated abnormalities in somatosensory evoked potentials (Furlong et al., 1990; Shagass et al., 1978; Josiassen et al., 1988; Norra et al., 2004; Waberski et al., 2004) and evoked fields (Reite et al., 2003; Thoma et al., 2007; Huang et al., 2010) in schizophrenia, few have good time resolution or are able to postulate specific mechanisms.

Evoked potential/evoked field studies involving neocortical driving using rapidly repeating stimuli which evoke a steady-state response (SSR) are a metric that provides both high time resolution as well as a likely mechanism underlying the generation of the responses. The phase control of individual SSR components in auditory and visual domains has been suggested as being a representation of neocortical GABAergic activity of interneurons which control layer 3 pyramidal cell firing in the sensory cortex (McBain and Fishan, 2001). In a study demonstrating increased corticomotoneuronal excitability in response to somatosensory stimulation (Kaelin-Lang et al., 2002), it was found that the GABA_A receptor agonist lorazepam blocked the effect whereas neither placebo nor dextromethorphan had any effect. The authors speculate that this pharmacologic modulation of the inhibitory cortical GABAergic neurotransmission system might explain the reduction in excitability and supports the general concept of GABAergic mediation of somatosensory cortex.

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Intertrial phase control of the SSR (termed phase-locking factor or PLF) provides a high resolution measure of the accuracy of neocortical timing mechanisms, abnormalities in which have been previously found in both auditory and visual domains in schizophrenia (Teale et al., 2008; Brenner et al., 2009). In the auditory realm the stimuli are often 40-Hz click trains or tones in which amplitude is modulated by 30–50-Hz sine waves. In the visual context stimuli may be light flashes or checkerboard alternation occurring in the 7–30 Hz range. In our case we utilized a tactile stimulation rate of 25 Hz, which was informed by a number of previous studies. The optimum frequency for vibrotactile steady state stimulation is probably somewhat variable by individual, but several studies have demonstrated good SSR responses with frequencies in the medium to high beta range. Snyder (Snyder, 1992) found the best signal-to-noise ratio to be associated with 26-Hz stimulation using an 8-cm diameter mechanically shaken sphere that engaged all fingers and the palm. Tobimatsu and colleagues (Tobimatsu et al., 1999) describe maximum response to 21-Hz oscillation using a 9-cm spherical shell, and Nangini and colleagues (Nangini et al., 2006) reported good results with finger stimulation using 22 Hz driving a bladder type stimulator with the right index finger. We performed several pilot studies utilizing our tactile stimulator and found the optimal SSR response at 25 Hz. This was done with three volunteers in our lab using stimulus rates from 10 to 100 Hz in steps of 5 Hz. All three subjects demonstrated maximal response at 25 Hz.

In this study we utilized the somatosensory SSR to tactile stimulation as a method to estimate somatosensory neocortical timing mechanisms central to motor control, a method, to our knowledge, not previously reported in schizophrenia. We hypothesized that the phase-locking factor and related evoked amplitude would be diminished in subjects with schizophrenia as they have been in the other sensory modalities investigated to date.

2. Methods

2.1. Subjects

We studied 13 patients with schizophrenia (six female, mean age 46 ± 7). We compared their data with that of 18 comparison subjects (eight female, mean age 40 ± 12). There was no statistically significant difference in age between the groups ($t(30) = 1.6024, p = 0.1195$). Diagnosis was determined using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) (American Psychiatric Association, 2000) criteria based on structured diagnostic interviews, the Structured Clinical Interview for DSM-IV-TR and the Diagnostic Interview for Genetic Studies (SCID and DIGS) (First et al., 1995; Nurnberger et al., 1994), and information obtained from medical records. All subjects received a full explanation of the experimental procedures in accordance with the guidelines of the Colorado Multiple Institutional Review Board, and signed informed consent documents to that effect. All patients with schizophrenia were taking antipsychotic medications. Nine were taking only atypical antipsychotic, two were taking typical antipsychotics only (haloperidol, perphenazine), and two were taking both typical and atypical antipsychotics. Handedness was determined by the Annett Handedness Scale (Annett, 1985). Both groups were primarily right-handed (mean control score 0.61, mean patient score 0.41). Table 1 below lists the psychotropic medications and their olanzapine-equivalent dosage where available (Gardner et al., 2010).

2.2. Stimuli

Tactile stimuli delivered to the index finger tips of each hand were produced by a piezoelectrically operated Braille cell stimulator modified as appropriate for this application (METEC AG/TeleSensory Corp., Stuttgart, Germany). Eight piezoelectrically operated plastic rods (each 1.0-mm diameter) were activated in unison covering an area of 4×9 mm. The cell was encased in a 6-mm-thick acrylic box, and a 12-mm ball end mill was used to create a finger-tip sized cutout over the rod array. The index finger of each hand was placed over this cutout and held in place by tape. Displacement of rods upon activation was about 1 mm without load. Tactile stimuli were delivered at 25 Hz in trains of 500-ms duration. Stimulus trains were repeated every 2.0 s for at least 200 trials for each finger-tip. Each

Table 1
Psychotropic Medications.

Subject	Psychotropic medications	Olanzapine equivalent (mg/day)
1	Clonazepam, ziprasidone	30
2	Olanzapine	20
3	Clozapine, risperidone	30
4	Aripiprazole	3.4
5	Alprazolam, olanzapine, sertraline	20
6	Aripiprazole, haloperidol, olanzapine, sertraline	53.4
7	Clozapine	12.5
8	Clozapine, fluphenazine	21.7
9	Perphenazine	10
10	Haloperidol	30
11	Clonazepam, clozapine, quetiapine	8.1
12	Clozapine, risperidone	No dosage available
13	Risperidone	10

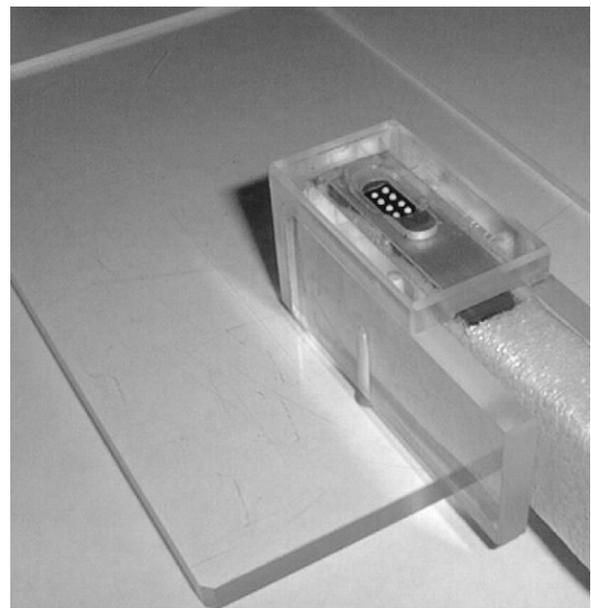


Fig. 1. Braille Cell in Acrylic Housing with one layer Cu shielding. The foam layer around the cell helped to reduce sound transmission. A second layer of Cu shielding was applied over the acrylic after this photo was taken and a 12-gauge ground strap was connected between the unit and the MSR ground.

individual tactile stimulus consisted of the plastic rod ensemble compressing the skin for 20 ms followed by the withdrawal of the rods for 20 ms; thus, there was, in addition to the tactile/pressure stimulus every 40 ms, a skin deformation stimulus every 20 ms or 50 Hz.

It should be noted that this device is capable of generating a capacitively coupled artifact unless proper shielding and grounding arrangements are made. We used a layer of copper foil around both the cell and the acrylic enclosure and a 12-gauge braided copper ground strap. The enclosed device is shown in Fig. 1. Approximately midway through the experiment, a failure in the outer shield and ground, which went undetected for a few weeks, produced a small frontal artifact that resulted in the rejection of four subjects with schizophrenia and seven normal control subjects.

2.3. Magnetoencephalographic (MEG) recording

Magnetic evoked fields were recorded with subjects in the supine position using a whole head neuromagnetometer (Magnes 3600 WH, 4D-Neuroimaging, San Diego, USA) while subjects watched a video movie with sound delivered by acoustically isolated (> 30 dB background attenuation, 125–8 kHz) foam ear inserts. Data were acquired in epochs of 1000-ms duration with a 300-ms pre-stimulus baseline using a sampling rate of 678.17 Hz and an analog bandwidth of 0.1–200 Hz. The establishment of a head frame coordinate system (and the registration of the sensor coils within it) was accomplished by securing small

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