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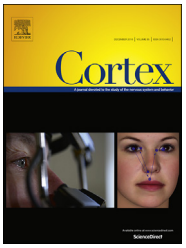

Research report

Altered cortical processing of motor inhibition in schizophrenia

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ABSTRACT

Inhibition is considered a key mechanism in schizophrenia. Short-latency intracortical inhibition (SICI) in the motor cortex is reduced in schizophrenia and is considered to reflect locally deficient γ-aminobutyric acid (GABA)-ergic modulation. However, it remains unclear how SICI is modulated during motor inhibition and how it relates to neural processing in other cortical areas. Here we studied motor inhibition Stop signal task (SST) in stabilized patients with schizophrenia ($N = 28$), healthy siblings ($N = 21$) and healthy controls ($n = 31$) matched in general cognitive status and educational level. Transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) were used to investigate neural correlates of motor inhibition.

SST performance was similar in patients and controls. SICI was modulated by the task as expected in healthy controls and siblings but was reduced in patients with schizophrenia during inhibition despite equivalent motor inhibition performance. fMRI showed greater prefrontal and premotor activation during motor inhibition in schizophrenia. Task-related modulation of SICI was higher in subjects who showed less inhibition-related activity in pre-supplementary motor area (SMA) and cingulate motor area. An exploratory genetic analysis of selected markers of inhibition (GABRB2, GAD1, GRM1, and GRM3) did not explain task-related differences in SICI or cortical activation. In conclusion, this multimodal study provides direct evidence of a task-related deficiency in SICI modulation in schizophrenia likely reflecting deficient GABA-A related processing in motor cortex. Compensatory activation of premotor areas may explain similar motor

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inhibition in patients despite local deficits in intracortical processing. Task-related modulation of SICI may serve as a useful non-invasive GABAergic marker in development of therapeutic strategies in schizophrenia.

1. Introduction

Inhibition is fundamental for cognitive control and the ability to stop a response when a rapid change in plan is required for adaptive behaviour (Aron, Robbins, & Poldrack, 2014; Goldman-Rakic, 1996). Deficits in the inhibition of ongoing or planned physical responses or actions (motor inhibition) have been shown in schizophrenia in both oculomotor (Hutton & Ettinger, 2006; Krebs et al., 2001) and manual motor tasks (Davalos, Compagnon, Heinlein, & Ross, 2004; Enticott, Ogloff, & Bradshaw, 2008; Huddy et al., 2009; Thakkar, Schall, Boucher, Logan, & Park, 2011). These findings indicate that impaired motor inhibition is one of the important traits of the disorder. However, some studies failed to report motor inhibition deficits (Badcock, Michie, Johnson, & Combrinck, 2002; Rubia et al., 2001) suggesting that some patients may not have impaired inhibition or could compensate for these deficits.

In the cortex, inhibition is mainly mediated by the neurotransmitter γ-aminobutyric acid (GABA) and its role in schizophrenia is deemed a key mechanism (Lewis, 2014; Mueller, Remedies, Haroutunian, & Meador-Woodruff, 2015). Paired-pulse transcranial magnetic stimulation (TMS) over primary motor cortex (M1) allows measurement of short-latency intracortical inhibition (SICI) (Kujirai et al., 1993) and studies suggest that SICI reflects GABA-A receptor function (Di Lazzaro et al., 2006). Reduced resting levels of SICI have been shown in schizophrenia, adding neurophysiological support for GABAergic dysfunction (Bunse et al., 2014; Fitzgerald, Brown, Daskalakis, & Kulkarni, 2002; Mehta, Thirthalli, Basavaraju, & Gangadhar, 2014; Rogasch, Daskalakis, & Fitzgerald, 2014; Takahashi et al., 2013; Wobrock et al., 2008). However, how SICI is modulated during motor inhibition in schizophrenia remains unstudied and its value as a trait or state marker is unknown, requiring studies in first-degree relatives of patients.

Motor inhibition is controlled by local inhibitory mechanisms in M1 and by a cortico-basal ganglia network including the prefrontal and premotor cortex and the basal ganglia (Aron & Poldrack, 2006). While, functional magnetic resonance imaging (fMRI) studies in schizophrenia show altered prefrontal, premotor and basal ganglia activation patterns during motor inhibition tasks (Hughes, Fulham, Johnston, & Michie, 2012; Kaladjian et al., 2007; Rubia et al., 2001; Zandbelt, van Buuren, Kahn, & Vink, 2011), a description of alterations in the cortical network together with local intracortical measures in M1 is lacking.

The purpose of our study was to explore the neural control of motor inhibition in schizophrenia. We used the Stop signal task (SST), similar to that of Coxon, Stinear, and Byblow (2006) and adapted to fMRI and TMS, in treated and untreated persons with schizophrenia, non-psychotic siblings and healthy controls. We hypothesized that reduced SICI, at the intracortical level, would be associated with impaired motor inhibition in patients. At the network level, we predicted that prolonged motor inhibition times would be related to reduced fMRI activity in regions of interest (ROIs) in the cortical inhibition network. Finally, since there is a genetic contribution to GABAergic dysfunction in schizophrenia (Addington et al., 2005; Zhao et al., 2006), we also explored whether motor inhibition or its neural correlates could be modulated by genotypic variations in key enzymes of the GABA/glutamate system possibly involved in schizophrenia.

2. Material and methods

2.1. Participants

Twenty-eight stabilized patients with schizophrenia or schizoaffective disorder (DSM IV) [24 males, age: 32 ± 6.7 years (mean ± SD)] (Scz), 21 healthy siblings (9 males, 31.5 ± 9.6 years) (Sib) and 31 healthy control subjects (16 males, 30.3 ± 7.7 years) (Con) were recruited at the Sainte Anne Hospital. Twenty-two patients were on stable (>3 months), atypical anti-psychotic medication (6 patients taking clozapine) and seven patients were non-medicated (for at least 6 months). Patients on mood stabilizers, antidepressants or benzodiazepines were excluded. The mean delay from the last hospitalisation was 4.8 ± 2.8 years, with 6 subjects never hospitalized (for clinical characteristics of patients, see Table 1). All subjects were right handed. Siblings came from supportive family groups mostly not related to recruited patients, and healthy controls from the community. Groups were matched for age, years of education, but not for gender (Table 1). Subjects were screened with the Diagnostic Interview for Genetics Studies (DIGS 3.0, French version, 2003) to attest the diagnosis and exclude co-morbidities in patients, including addiction, and to exclude psychiatric or neurological disease and substance abuse in siblings and controls. We also excluded siblings with an axis one disorder in the anamnesis. Subjects with contraindications to MRI and TMS (e.g., epilepsy, pacemaker or other metal implants) were excluded. The study received ethical approval from our local ethics committee (CPP Cochin, Ile de France III). All subjects provided informed and written consent and received 230€ for their participation.

After inclusion in the study the 80 subjects underwent a clinical assessment, blood sampling, and MRI. Behavioural and TMS experiments were performed on another day. We excluded aberrant responses and poor quality of recordings from the analysis: 74 (93%) subjects successfully completed the behavioural task (27 Con, 20 Sib, 27 Scz), 70 (88%) subjects