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Impairments of event-related magnetic fields in schizophrenia patients with predominant negative symptoms

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ABSTRACT

Recently there is a growing understanding that patients suffering from negative symptoms of schizophrenia represent a distinct patient population. However, despite the abundance of EEG studies characterizing schizophrenia patients in general, only a handful of studies have focused on the electrophysiological correlates of negative symptoms. The current study examined whether the impairments in event-related magnetic fields (ERFs) commonly reported in heterogeneous groups of patients with mixed positive and negative symptoms also occur in patients with predominantly negative symptoms, and investigated their correlation to clinical symptoms and cognitive deficits. Twenty schizophrenia patients suffering from predominant negative symptoms and 25 healthy subjects underwent neuropsychological and electromagnetic assessments. ERFs were recorded during a three-stimuli novelty oddball and a sensory gating paradigm, and M50, P300m and Novelty-P3m components were investigated. Patients displayed impaired M50 ratios, reduced left P300m and frontal Novelty-P3m amplitudes. These electromagnetic measures correlated significantly with the severity of negative symptoms (SANS scale). The electrophysiological abnormalities which have been proposed as candidate biomarkers for schizophrenia are also manifested in patients with predominantly negative symptoms.

1. Introduction

Negative symptoms in schizophrenia predict an unfavorable clinical outcome and are often indicative of poorer social, occupational, and global outcomes (Milev et al., 2005). They are particularly correlated with cognitive deficits but occur independently of positive symptoms, and therefore may make a unique contribution to the neural and cognitive deficits observed in schizophrenia (Harvey et al., 2006). In this study we aimed to investigate the electromagnetic and neurocognitive aspects of negative symptoms.

Event-related potentials (ERPs) are the average EEG signals time-locked to a stimulus or event and provide sensitive and reliable measures of the neuronal processes underlying cognition (Luck et al., 2011). ERPs abnormalities in various components have been commonly associated with schizophrenia, including P50 and P300 (Bramon et al., 2004). These abnormalities show high heritability, often appear in unaffected family members and have been proposed as candidate biomarkers for this illness (Turetsky et al., 2007; Luck et al., 2011; Oertel-Knöchel et al., 2011). The ERP components appear to involve different underlying cognitive and neural processes that are deficient in schizophrenia. Abnormal P50 suppression has been taken as a vulnerability marker for the sensory gating deficits (Potter et al., 2006). Reduction in P300 amplitude is taken to index deficits in the allocation of attentional resources and working memory, and has been linked to neuronal activity of frontal and temporoparietal brain regions (Ford, 1999). Two other recent candidate biomarkers for schizophrenia are N100 amplitude reduction (Rosburg et al., 2008) and impairments in the novelty-P3 or P3a (Cortiñas et al., 2008). N100 amplitude reflects auditory perception and is affected by activity in the primary and secondary auditory cortex; however, the findings regarding this component in schizophrenia are inconsistent (Rosburg et al., 2008 The P3a is thought to reflect orienting and involuntary shifts of attention as well as novelty processing which are related to activity in frontal brain regions (Friedman et al., 2001).

Recently there is a growing understanding that patients suffering from negative symptoms of schizophrenia represent a distinct patient population (Kirkpatrick and Galderisi, 2008). However, despite the abundance of EEG studies characterizing schizophrenia patients in general (Ford et al., 2012), only a handful of studies have focused on the electrophysiological correlates of negative symptoms (Bramon et al., 2004; Umbricht and Krljes, 2005). In addition, most findings concerned heterogeneous groups of patients including both positive and negative symptoms, and have

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mixed reports of the correlation between ERPs and negative symptoms scales. A small number of studies have investigated patient groups with predominant negative symptoms. Patients with deficit schizophrenia, that is, with enduring, primary (or idiopathic) negative symptoms, exhibit impaired P50 sensory gating ratios (Frodl et al., 2002; Louchart-de la Chapelle et al., 2005; Santos et al., 2010). However, P50 abnormalities were found to correlate with negative symptom severity in some (Louchart-de la Chapelle et al., 2005; Thoma et al., 2005) but not in other studies (Adler et al., 1990; Potter et al., 2006). N1 appears to be impaired in deficit patients as well, and not related to positive symptoms (Mucci et al., 2007; Boutros et al., 2009). Significant reductions in P300 amplitude were reported for negative-profile patients relative to healthy controls but not for patients with a positive-profile (Liu et al., 2004). The relationship between ERP impairments and negative symptoms is still inconclusive and there is great variance between studies in the effects reported.

A related issue concerns hemispheric asymmetries in schizophrenia and their manifestation in ERP components. Asymmetrical P300 reduction has been frequently reported with smaller amplitudes over the left temporal regions (Jeon and Polich, 2001), but not in all studies (Ford et al., 2000). Two studies reported P300 reductions over left hemisphere sites only in non-deficit patients (Turetsky et al., 1998; Mucci et al., 2007), but a reduction in right P300 in deficit patients. A more recent study found decreased P300 activity that correlated with negative symptoms, predominantly at left hemisphere sources (Kim et al., 2014). Thus, it is important to disentangle the various P300 sub-components and lateralization to understand their relation to the clinical aspects.

Most electrophysiological studies in schizophrenia have used EEG. Magnetoencephalography (MEG) may be a more suitable technique to identify presumably lateralized cortical generators, as the magnetic signals are not substantially distorted by volume conduction like the electrical signals. For example, MEG recordings have shown that the P50 signal observed at Cz is a function of the activity of two electrical sources localized to the bilateral temporal gyrus (Onitsuka et al., 2000). Another study (Thoma et al., 2003) demonstrating the advantage of MEG in discriminating lateralized sources of ERPs found that M50 (the magnetic counterpart of P50) showed hemisphere-specific relationships with neuropsychological and clinical measures that were not detectable by EEG. Thus, MEG may be a more sensitive measure for evaluating lateralized cortical generators of M50 or other components showing lateralized sub-components and their relation to negative and cognitive symptoms.

The objective of the current study was to examine various auditory event-related magnetic fields (ERFs), which have been commonly associated with schizophrenia, in a homogenous group of schizophrenia patients with predominantly negative symptoms. A paired-click paradigm was used to elicit the M50 component and assess sensory gating; a process which, so far, has shown inconsistent results in patients with negative symptoms. A three-stimulus novelty oddball was used to measure the Novelty-P3m and P300m components. Although there are indications of a possible relation between negative symptoms and impairments in response to novelty (Wolf et al., 2008), it has not been studied with EEG/MEG in patients with predominant negative symptoms. We predicted that patients with predominant symptoms would show abnormal ERF waveforms which would correlate with the severity of negative symptoms.

Table 1
Demographic and clinical characteristics of schizophrenia patients and control subjects.

Variable	Control subjects ($N=25$)		Schizophrenia patients ($N=20$)		Analysis	
	Mean	S.D.	Mean	S.D.	Statistic	p
Age	29.92	7.47	29.30	6.30	$t=0.296$, d.f.$=43$	0.768
Education (years)	13.22	2.52	12.05	2.82	$t=1.460$, d.f.$=43$	0.152
Parental education (years)	13.08	3.12	11.93	3.90	$t=1.099$, d.f.$=43$	0.277
Male/female ratio	18/7		15/5		$\chi^2=0.051$, d.f.$=1$	0.821
Handedness (left/right)	4/21		3/17		$\chi^2=0.008$, d.f.$=1$	0.927
Smoker/non-smoker ratio	7/18		7/13		$\chi^2=0.254$, d.f.$=1$	0.617
	Mean	S.D.	Mean	S.D.		
Duration of illness (years)			10.25	3.88		
Illness onset			19.05	5.58		
SANS						
Affective flattening			17.95	5.28		
Alogia			13.65	3.91		
Avolition/apathy			12.05	2.43		
Anhedonia/asociality			16.40	3.03		
Total			60.05	14.26		
PANSS						
Negative			31.50	6.94		
Positive			11.25	2.97		
General			46.25	11.87		
Total			89.00	20.41		
Medication						
Atypical antipsychotics			75% (15)			
Clozapine (727 ± 372.5 mg)			5			
Quetiapine (814 ± 415.6 mg)			4			
Olanzapine (310.3 ± 282.9 mg)			2			
Risperidone (236.4 ± 188.5 mg)			2			
Aripiprazole (196 mg)			2			
Quetiapine (66.7 mg)+Risperidone (250 mg)			1			
Typical antipsychotics			20% (4)			
Fluphenazine (825 ± 1096 mg)			3			
Haloperidol (250 mg)			1			
Both			5% (1)			

SANS=scale for the assessment of negative symptoms (34); PANSS=positive and negative syndrome scale (35).