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Movement-related potentials point towards an impaired tuning of reafferent sensory feedback by preceding motor activation in schizophrenia

Stephan Bender [a,b,c,*], Johannes Schröder [d], Christine Freitag [b], Veit Roessner [c], Franz Resch [e], Matthias Weisbrod [a,f]

[a] Section Experimental Psychopathology - Neurophysiology, Psychiatric Hospital, University of Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany
[b] Department of Child and Adolescent Psychiatry, Johann-Wolfgang Goethe University Frankfurt, Deutschordenstraße 50, 60528 Frankfurt a. M., Germany
[c] Department of Child and Adolescent Psychiatry, Medical School Carl Gustav Carus, Dresden University of Technology, Fetscherstraße 74, 01307 Dresden, Germany
[d] Section Gerontopsychiatry, Psychiatric Hospital, University of Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany
[e] Department for Child and Adolescent Psychiatry, University of Heidelberg, Blumenstraße 8, 69115 Heidelberg, Germany
[f] SRH-Klinikum Karlsbad-Langensteinbach, Psychiatric Hospital, Guttmannstraße 1, D-76307 Karlsbad, Germany

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ABSTRACT

The link between focal motor system activation and reafferent sensory feedback is thought to be crucial for the perception that a movement is *actively* performed. In this article, we examine how schizophrenia affects the relationship between motor and somatosensory system activation. Movement-related potential source analysis allowed us to separate and compare motor activation deficits and reafferent feedback processing. We analyzed lateralized movement-related potentials during choice reaction movements in 16 subjects with schizophrenia/schizoaffective disorder. These subjects had partial remissions with predominantly negative symptoms and were compared to an age-matched healthy control group. In the schizophrenia/schizoaffective group, dipole source analysis indicated a significantly reduced lateralized sensorimotor activation immediately preceding movement execution. In contrast, activation by reafferent feedback was relatively unimpaired. Subjects with schizophrenia/schizoaffective disorder lacked a focal motor and reafferent sensory processing correlation, which can be identified through a significantly different regression slope from healthy controls. Reduced action-related motor system activation in subjects with schizophrenia/schizoaffective disorder was associated with preserved activation by reafferent sensory feedback. Most importantly, motor-sensory tuning, i.e. a specific enhancement of sensory information necessary to monitor movements, could not be found in subjects with schizophrenia/schizoaffective disorder. Our data provide further evidence for disturbed motor-sensory interactions in schizophrenia.

1. Introduction

In order to ensure that an action is successfully completed, movements must be compared with sensory feedback about the actual movement course (Nelson, 1996). On one hand, inappropriate reflexes can be cancelled by inhibition of reafferent sensory activity (Cullen, 2004). On the other hand, corollary discharges can also govern complex feedforward processes that involve finely tuned proprioceptors that modulate their sensitivity during the course of a movement (Chapin and Woodward, 1982; Rossignol et al., 2006; Crapse and Sommer, 2008). An efficient motor corollary discharge should selectively enhance the part of proprioceptive and somatosensory feedback that is relevant to monitor the movement course (Nelson, 1996; Rossignol et al., 2006; Poulet and Hedwig, 2007; Crapse and Sommer, 2008).

Corollary discharges are related to a variety of functions during motor-sensory cycles from the optimization of a motor performance to the distinction of active from passive movements (Nelson, 1996). Pronounced deficits in motor-sensory interactions, i.e. the comparison of the programmed movement to reafferent feedback, may finally lead to the erroneous conclusion that an internally generated action was externally generated (Frith, 1987; Feinberg and Guazzelli, 1999; Blakemore, 2003). Neurological soft signs reflecting deficient motor-sensory integration are comparatively subtle and are more common in subjects suffering from schizophrenia. Therefore, in the present study we examined how the motor-sensory cycle is affected by schizophrenia in order to elucidate motor-sensory interactions in the disease. This is of special interest because deficits in the 'forward model', i.e. the prediction of the sensory consequences of their actions, have been described in schizophrenia (Franck et al., 2001; Fourneret et al., 2002; Posada et al., 2007; Farrer et al., 2008).

Movement-related potential dipole source analysis (Toma et al., 2002) provides the necessary temporal and spatial resolution to separate these different movement stages. However, movement-related

* Corresponding author at: Child and Adolescent Psychiatric Hospital, University of Dresden, Fetscherstraße 74, D-01307 Dresden, Germany. Tel.: +49 351 458 7072; fax: +49 351 458 5754.
E-mail address: Stephan.Bender@uniklinikum-dresden.de (S. Bender).

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potential source analysis has not yet been performed in subjects with schizophrenia. Smaller Bereitschaftspotential amplitudes seen in patients with schizophrenia (Singh et al., 1992; Dreher et al., 1999; Northoff et al., 2000) are understood to reflect volitional deficits (Westphal, 2003). Although significance was not reached in all studies, a reduction of lateralized readiness potential amplitude in subjects suffering from schizophrenia (Luck et al., 2009; Karayanidis et al., 2006; Kieffaber et al., 2007; Mathalon et al., 2002) has been established. However, these deficits have not yet been related to the processing of reafferent feedback.

A source analysis separating and comparing motor and reafferent sensory potential components could yield important additional information about a possible misfit of the motor model and actual movement perception. In the current study, we examined lateralized movement-related potentials in young subjects with schizophrenia/schizoaffective disorder and predominantly negative symptoms, after remission of acute psychosis compared to an age-matched healthy control group. We used *reaction* button presses that permitted 1) the standardization of movements, and 2) the minimization of overlaps with delayed Bereitschafts potential resolution. Moreover, we employed a *choice* reaction time task that produced ipsilateral motor cortex inhibition instead of co-activation (Vidal et al., 2003). This paradigm provides an additional model of a corollary discharge, where ipsilateral motor cortex must be deactivated by transcallosal inhibition.

We hypothesized that normal control subjects would show a correlation between lateralized focal motor system activation (iMP′ amplitude) and lateralized focal reafferent sensory feedback processing (fpMP′ amplitude). But subjects with schizophrenia/schizoaffective disorder would show a reduced or absent correlation between these parameters. Such a reduced correlation would reflect a possible corollary discharge deficit. Focal motor system activation could influence subsequent focal reafferent sensory processing in healthy controls but not in subjects with schizophrenia/schizoaffective disorder. Inter-individual differences in the degree of lateralized motor processing should lead to a strong correlation of motor and sensory activation in the presence of unimpaired motor-sensory tuning, while the correlation should be absent without motor-sensory tuning. This hypothesis of a motor-sensory disconnection in schizophrenia was based on previous findings of 'disconnectivity' in schizophrenia (Ford et al., 2002; Uhlhaas and Singer, 2010).

2. Methods

2.1. Subjects

A Structured Clinical Interview (SCID) established diagnoses according to the DSM-IV. All patients were recruited from an inpatient population at the University Hospital, Heidelberg and were examined after a partial remission of positive symptoms. Symptom assessment was undertaken before the EEG recordings. All subjects were right-handed.

In the schizophrenia/schizoaffective disorder group ($n=16$), nine subjects were schizoaffective, four suffered from the paranoid subtype, two from the disorganized subtype, and one from the undifferentiated schizophrenia subtype. Subjects with a schizoaffective disorder were included in order to investigate whether they would differ qualitatively from subjects with schizophrenia. Twenty age-matched young healthy adults were recruited (Table 1).

All subjects with schizophrenia/schizoaffective disorder were on stable medication. Most subjects received atypical antipsychotic medication: clozapine ($n=6$), amisulpride ($n=3$), olanzapine ($n=3$), risperidone ($n=1$), quetiapine ($n=1$), ziprasidone ($n=1$), aripiprazole ($n=1$). One patient was on a typical neuroleptic. Schizoaffective subjects received tricyclic, SSRI, or SNRI antidepressant medication.

We chose to examine medicated subjects because previous studies established that extrapyramidal motor side effects of antipsychotic medication could not account for differences in Bereitschaftspotential, which is contingent on negative variation (Verleger et al., 1999) or lateralized sensorimotor cortex activation (Braus et al., 1999). In addition, the amplitude of lateralized movement-related potentials is not altered in Parkinson's patients, who suffer from severe impairments in dopaminergic neurotransmission (Wascher et al., 1997; Plat et al., 2000).

Exclusion criteria were neurological co-morbidity and other psychiatric diseases. All subjects passed a test for color vision, and provided written informed consent. The study design was approved by the local ethics committee, and was conducted according to the Declaration of Helsinki.

2.2. Task

Subjects were given a choice reaction task while looking at a computer screen from a distance of 60 cm. Subjects had to recognize the font color of 16 different words, each presented for 150 ms. The test presented colors in red, yellow, green, and blue. Subjects were asked to indicate the color of each word by pressing the corresponding button on a response pad with colored buttons: red = left middle finger, yellow = left index finger, green = right index finger, blue = right middle finger. Fingers were placed on the buttons throughout the recording and the subjects were asked to respond as quickly as possible. The sequence of colors was randomized and each color appeared as often as another. The words consisted of 16 neutral, 16 negative and 16 positive short adjectives. Negative and positive words were taken from 3 different German mood questionnaires: 1. the 'list of adjectives' ('Eigenschaftswörterliste'; Janke and Debus, 1978), 2. the 'multidimensional mood questionnaire' ('Mehrdimensionaler Stimmungsfragebogen'; Hecheltjen and Frank, 1973) and 3. the 'scale for self-assessment of current mood' ('Skala zur Selbsteinschätzung der aktuellen Stimmung'; Hampel, 1971). Negative words were selected from the subscales 'depressed mood' and positive words from the subscales 'elevated mood'. The neutral words were taken from the 'Handbook of norms for German words' (Handbuch deutschsprachiger Wortnormen; Hager and Hasselhorn, 1994). All words were matched for the word frequency, word length and the initial letter of the word. Emotional valence did not influence reaction times significantly among any of our subjects and was counterbalanced by left and right hand responses. Emotional valence did not influence the lateralized brain potentials either (not shown). As such, the task can be described as a difficult choice reaction task. The interstimulus interval was 2000–2400 ms (randomized, 100-ms steps). Every word was presented eight times over the course of the 384

Table 1
Subjects – clinical characteristics (mean ± standard deviation).

	N	Age [years]	Gender	SCID	BPRS	SANS	SAPS	BDI	CDSS	EHI
Schizophrenic/ schizoaffective disorder	16	29.5 ± 9.6 range 19–51	9 m, 7 f	7 schizophrenic 9 schizoaffective	37.1 ± 15.3 40.1 ± 11.2	36.1 ± 27.2 31.9 ± 25.1	8.1 ± 14.0 7.0 ± 7.9	13.9 ± 12.5 22.8 ± 9.8	7.5 ± 6.5 8.9 ± 6.7	+92.7 ± 12.1
Young healthy adults	20	29.0 ± 8.0 range 19–45	9 m, 11 f	none	–	–	–	1.3 ± 1.4	–	+94.2 ± 11.2

m = male, f = female; SCID = Structured Clinical Interview for DSM IV; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; BDI = Beck Depression Inventory; CDSS = Calgary Depression Scale for Schizophrenia; EHI = Edinburgh Handedness Inventory, laterality quotient (all subjects ≥ +57).