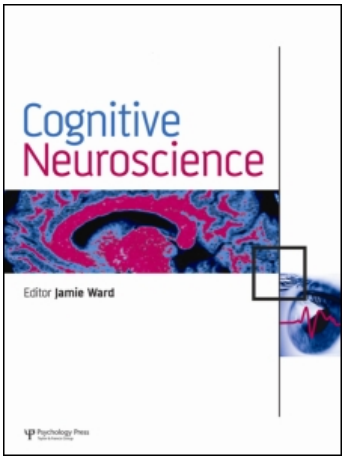

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The neural basis of disturbed efference copy mechanism in patients with schizophrenia

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Core psychopathological symptoms in patients with schizophrenia suggest that their sense of self may be disturbed. A disturbance in predictive motor mechanisms may be the cause of such symptoms. Ten patients with schizophrenia and ten healthy right-handed control subjects opened and closed their hand. This movement was filmed with an MRI compatible video camera and projected online onto a monitor. BOLD contrast was measured with fMRI. The temporal delay between movement and feedback was parametrically varied. Participants judged whether or not there was a delay. Patients were less sensitive to these delays than a matched control group. Comparing neural activation between the two groups showed a reduced attenuation of movement-sensitive perceptual areas in patients with increasing delay and a higher activation in the putamen in controls. The results provide further evidence that impaired efference copy mechanisms may contribute to the pathogenesis of schizophrenia and its first rank symptoms.

Keywords: Corollary discharge; Basal ganglia; Functional imaging; Psychiatry; Forward model.

INTRODUCTION

Disturbances of self are a main symptom of schizophrenic psychopathology. Patients often report that their thoughts and actions are controlled by external forces, and some hallucinationism, i.e., commenting and dialogizing voices seem to be misinterpretations of their own inner voice as an external voice. These first-rank symptoms are considered to be central to schizophrenia psychopathology (Leube & Pauly, 2008). First-rank symptoms raise questions about how people distinguish between self and nonself.

One neuropsychological proposal to explain this ability sees an important role for the sensory experiences resulting from self-generated actions and sensory experiences resulting from external sources (Feinberg, 1978; Frith, 1987; Malenka, Angel, Hampton, & Berger, 1982). The basic proposal is that psychosis is due to deficits in self-monitoring systems that normally enable one to distinguish between the products of self-generated actions or thoughts and those of other-generated actions or thoughts. Self-monitoring relies on forming predictions about the expected sensory consequences of one's action, triggered by a corollary

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discharge, and then subtracting this prediction from the actual sensory input. When predicted and observed consequences match, the observed consequences are experienced as self-generated. The contribution of efferent information to self-recognition is higher than information from other bodily sources, e.g., proprioception (Tsakiris, Haggard, Franck, Mainy, & Sirigu, 2005)

It has been hypothesized that patients with ego-disturbances and hallucinations cannot correctly compare the expected and observed consequences of an action and therefore have problems in identifying their actions and thoughts as the cause for events they perceive.

A part of the functionality of the efference copy mechanism is that predicted sensory feedback is attenuated. For example, a self-produced tactile stimulus is perceived as less ticklish than the same stimulus generated externally. In a functional magnetic resonance imaging (fMRI) study, brain activation was compared when subjects experienced a tactile stimulus that was either self-produced or externally produced. The neural activity of the somatosensory cortex was higher when the stimulus was externally produced compared to the condition when it was self-produced (Blakemore, Wolpert, & Frith, 1998).

There is also empirical evidence for the claim that a disturbed efference copy mechanism can contribute to symptomatology in schizophrenia. One study has demonstrated that tactile sensations following self-generated movements are attenuated in healthy subjects, but not in patients with paranoid-hallucinatory syndrome (Blakemore, Smith, Steel, Johnstone, & Frith, 2000). Further experiments have demonstrated that patients with schizophrenia with paranoid-hallucinatory syndrome who carried out simple joystick movements could not correct movement errors in the absence of visual feedback, although there were no clinical indications of a disorder of the motor system (Frith and Done, 1989; Malenka et al., 1982; Mlakar, Jensterle, & Frith, 1994). Patients with paranoid-hallucinatory syndrome and passivity phenomena (ego-disturbances) are also less sensitive to angular deviations between their actual hand movements and the visual consequences of these movements (Daprati et al., 1997; Franck et al., 2001). There is also a connection between auditory verbal hallucinations and the imprecision of the corollary discharge assessed by event-related potentials (Heinks-Maldonado et al., 2007).

In the current study we investigated whether different temporal delays (0–200 ms) between carrying out a simple repetitive movement and perceiving the visual feedback about these movements would change the pattern of activation in brain areas related to motor control and movement perception. Participants opened and closed their hand in a 0.5 Hz rhythm while being filmed by an fMRI-compatible video camera, and fMRI data were acquired. During short trials (3 s) participants received visual feedback of their movements (filmed by a video camera and projected on a monitor). Delays between movements and their visual consequences were parametrically varied across trials ranging from 0 ms to 200 ms. Participants' task was to report whether a delay was present or not. An earlier study on healthy subjects demonstrated for this task that activation in areas for movement perception in the superior temporal sulcus (pSTS) was positively correlated with the extent of the temporal delay. Conversely, the activation of a core area for motor control, the putamen, was negatively correlated with the temporal delay (Leube et al., 2003). This pattern of activation (a motor area generates signals that in turn modulate activation in perceptual areas) supported the assumption that the integration of a movement with its visual consequences may rely on a forward mechanism.

In the present study we asked whether patients with schizophrenia show the same or a different pattern of brain activations as healthy participants. If schizophrenic symptoms can be explained as a dysfunction of an efference copy mechanism, one would expect a different pattern. Dysfunctions in generating motor predictions should be reflected in reduced putamen activation in patients with schizophrenia. The lack of an accurate prediction, in turn, should lead to a reduced attenuation effect in perceptual areas for visual movement processing.

METHODS

Ten patients with schizophrenia and 10 healthy right-handed participants were recruited from the university hospital in Tuebingen. The patients with schizophrenia (5 male and 5 female, age 34.2 ± 8.5 years) were diagnosed according to DSM-IV criteria (Saß, 2003). All patients were treated with second-generation (atypical) antipsychotics in a hospital setting. All patients suffered from the paranoid subtype of the disease and were in partial remission after an acute psychotic episode (PANSS sum score 67.9 ± 14.2) with rather low positive symptoms (Kay, Fiszbein, & Opler, 1989). The healthy control participants (7 male and 3 female, age 27.7 ± 7.0) did not suffer from any psychiatric or medical disease. Patients and healthy controls were right-handed. Patients and control participants were fully briefed about the experimental procedures and

gave their written informed consent according to the Declaration of Helsinki.

All participants were instructed to open and close their right hand continuously and smoothly throughout the experiment while blood-oxygen-level-dependent (BOLD) contrast was measured with fMRI. They were also instructed to move at a pace of 0.5 Hz (opening and closing their hand once in 2 s) and not to touch their palm with their fingers in the closing position. All participants were able to perform the task before the scanning session started and fully complied with the instructions while performing the task in the scanner. The hand movements were filmed using an fMRI-compatible video camera. The images recorded by the camera could be projected online onto a screen that the participants viewed via a mirror.

During the experimental trials participants observed their own hand moving on the screen for 3 s. The video image was systematically delayed. The delay ranged from 0 to 200 ms (40-ms steps) and varied randomly from one trial to another. Participants' task was to report whether or not they perceived the performed and the observed hand movements as being synchronous. They indicated their choice after each trial by pressing one of two buttons with the left thumb. The time interval between trials was jittered, and ranged from 10 s to 14 s (mean 12 s). During this interval a still frame of the participant's hand was displayed on the screen. There were 120 trials in total, i.e., 20 trials at each level of delay.

The online temporal delays of the video stream were realized by a PC frame grabber card and custom software programmed in Microsoft Visual C. Picture frames were loaded on a ring buffer and re-entry occurred at time points between 0 and 200 ms in 40-ms intervals. Between trials, the last image frame was frozen so that participants observed their static hand while they continued with the rhythmic hand movement.

Scanning was performed with a Siemens 1.5 T scanner (Sonata). Functional images consisted of echo-planar image volumes which were sensitive to BOLD contrast (TE 40 ms, TR 2 s, flip angle 90°). The volume covered the whole brain with a 64×64 matrix and 22 slices with an in plane resolution of 3×3 mm^2. Three runs, consisting of 253 volumes, were acquired. To ensure that a steady state magnetization had been reached, the first six acquired volumes were discarded. A trigger signal from the scanner, the button press of the subject, and the onset of the stimuli were registered in a protocol, together with the timeline, on a separate computer. A T1 weighted data set (MP-RAGE; $1.5 \times 1 \times 1$ mm^3) was collected to serve as an anatomical reference.

For image preprocessing, SPM02 software (Wellcome Department of Cognitive Neurology, London) was used. All statistical analyses were performed with SPM05. The images of each subject were corrected for acquisition delay (slice timing) and were realigned by using the first scan of the block as reference. T1 anatomical images were co-registered to the mean of the functional scans and aligned to the SPM T1 template in the MNI space (Montreal Neurological Institute, mean brain). The calculated nonlinear transformation was applied to all images for spatial normalization. Finally, the images were smoothed with a 12 mm full-width, half-maximum (FWHM) Gaussian filter. The relationship between delay length and neural activation was calculated in a parametric analysis for each subject in a fixed effect model. The stimulus onset asynchronies (SOAs) from the protocol file were defined as events and convolved with the hemodynamic response function. In this approach events (delay lengths ranging from 0 to 200 ms) were modeled parametrically and contrast images for a positive and for a negative linear correlation calculated for each subject separately. Condition and subject effects were estimated according to the general linear model at each voxel in the brain space. These contrast images were then entered in a second-level model (simple *t*-test). Activations are reported if they exceeded a threshold of $p < 0.05$ corrected on the cluster level for the parametric contrasts ($p < 0.05$ on the single voxel level for the main effect).

RESULTS

Behavioural data

Subjects judged whether there was a temporal delay between their actual movements and the visual feedback displayed on the screen or whether both occurred simultaneously. Figure 1 shows these simultaneity judgments as a function of delay for patients and controls. Not surprisingly, the smaller the delay, the more likely participants were to perceive performed and perceived movement as being simultaneous. More interestingly, there was a significant difference between the patients and the healthy controls: Patients were more likely to perceive a delay even if there was no delay ($t = 2.21$; $p = 0.04$). Furthermore, patients' detection was significantly compressed. While the difference in detection rates between the no delay condition and the most extreme delay condition of 200 ms was 87% on average in healthy participants, it was only 67% in patients ($t = 2.38$; $p = 0.03$).

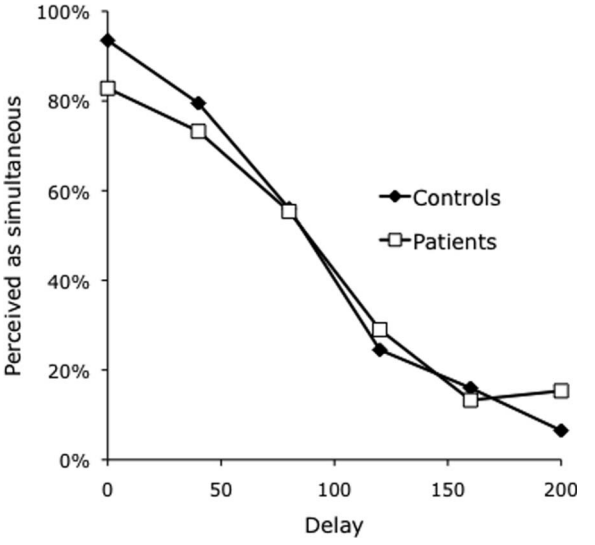

Figure 1. Simultaneity judgments as a function of temporal delay: The longer the delay, the smaller was the likelihood that the timing of performed and perceived movement was judged as simultaneous. Patients' detection function was compressed at both ends. They were significantly more likely to perceive a delay when, in fact, there was no delay.

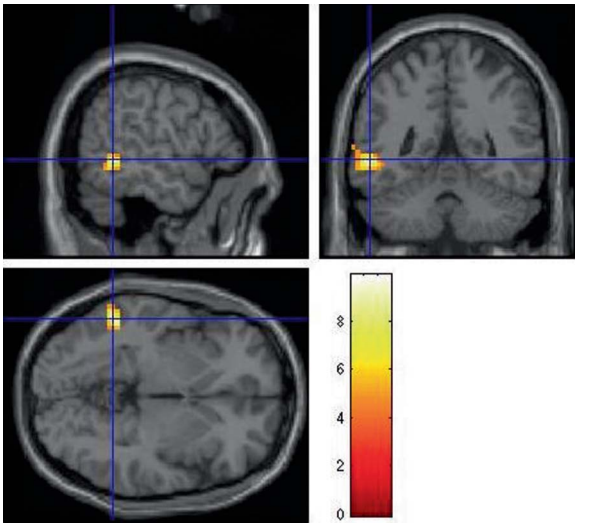

Figure 2. Brain area showing a positive correlation with the delay length in healthy subjects (MNI *x*, *y*, *z* mm –54 –48 –3). Maximum intensity projection (MIP) showing voxels in the left middle temporal lobe slightly anterior to the V5/MT complex. The contrast images from correlational analysis for each subject individually were entered into a second-level analysis (n=10).

FMRI data

Patients show reduced activation in sensorimotor and motor areas

A first analysis compared the neural activation in response to observing one's hand moving (main effect regardless of delay length between performed and observed movement) and watching a static hand (low level baseline) between patients with schizophrenia and healthy controls (contrast images of the main effect were entered into a between group comparison). Controls showed a higher activation in bilateral putamen and medial thalamus (see Table 1). There were no brain areas that were more active in patients.

Perceptual areas positively correlated with delay in patients and controls

Healthy controls showed a significant activation in a brain area lying in the left posterior temporal lobe at the borders of middle temporal gyrus, and supramarginal gyrus (MNI *x*, *y*, *z* mm –54 –48 –3; $Z = 4.62$; $p < 0.001$, cluster level corrected for multiple comparisons) that correlated positively with the delay length (see Figure 2). No significant positive correlations between delay length and brain activation was present in patients with schizophrenia. We could also confirm this result in a between group comparison where contrast images of the correlational analysis were entered. This analysis showed that healthy subjects exhibited a significantly higher positive correlation with delay length than patients with schizophrenia (MNI *x*, *y*, *z* mm –54 –48 –3; $Z = 6.58$; $p < 0.025$, FDR corrected for multiple comparisons).

Areas correlated with sensitivity for delays

The last analysis asked whether brain activations in patients and controls corresponded to a measure of discrimination ability that captures the extent to which the psychophysical detection functions were compressed at the ends (percent judged as being

TABLE 1
Results of a two-group comparison (Healthy controls v. Patients) of the main effect irrespective of delay length

Region	*MNI coordinates*	*Z-value*	*Voxel size*	*Voxel level* $p_{FDR\text{-}corr}$	*Cluster level* $p_{corrected}$
Left putamen	–21 12 –3	4.56	236	0.011	0.000
Left thalamus	12 –9 3	4.48	236	0.011	0.000
Right putamen	21 9 3	4.44	382	0.011	0.000
Right thalamus	12 –12 6	4.47	382	0.011	0.000

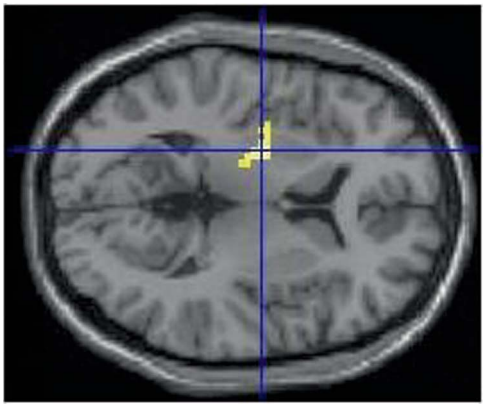

Figure 3. Brain area showing a positive correlation with the extent of compression (MNI *x*, *y*, *z* mm –24, –9, 6). MIP showing voxels in the left putamen.

simultaneous in the 200 ms delay condition minus percent judged as being simultaneous in the 0 ms delay condition). Across patients and controls there was an area in the left putamen (MNI *x*, *y*, *z* mm –24, –9, 6; $Z = 3.96$; $p = 0.010$, cluster level corrected for multiple comparisons) that significantly correlated with the extent of the compression (Figure 3). In other words, the less sensitive a participant was for the delays between a movement and its visual consequences, the lower was the activation in this area.

DISCUSSION

We found evidence for a disturbance of efference copy mechanisms in patients with schizophrenia. The patients' reduced ability to predict the timing of the visual consequences of their own hand movements is reflected in their reduced ability to identify synchronous visual feedback as reflecting the movement of their own hand (no delay condition). It is also reflected in their reduced ability to reject visual movement information as not reflecting their own movements at longer delays.

There were also differences in brain activation between patients with schizophrenia and control participants. First, patients with schizophrenia showed less activation in the putamen, a brain area that has previously been identified as generating predictions about the time at which the visual consequences of movements should occur (Leube et al., 2003). This interpretation is supported by the present finding that left putamen activation correlated with participants' overall sensitivity for temporal delays between movements and their visual consequences. Second, a correlation between delay length and activation in lateral occipitotemporal brain areas for visual movement processing in the middle temporal gyrus (Jung et al., 2009) between the V5/MT complex (Watson et al. 1993; Lanyon et al. 2009) and STS was only observed in healthy participants but was absent in patients with schizophrenia. This suggests that attenuation of visual input through motor predictions is absent or reduced in patients with schizophrenia. We measured this attenuation in left temporal lobe in contrast to previous studies that localized it in the right hemisphere (Farrer et al., 2004; Leube et al., 2003). Although a lateralization may be suggestive from a neural network stance as a left side putamen fits well with a left side temporal lobe involvement, we can't rule out the possibility that there is no lateralization at all. Possibly the effects are due to contingency within the rather small study populations. This would explain different lateralization effects between different studies.

We cannot rule out a certain influence of neuroleptic medication although all patients were treated with atypical neuroleptics exercising only a weak influence on the motor system.

The results support previous findings that the psychotic symptoms in schizophrenia are related to a disturbed efference copy mechanism that is crucial for predicting the sensory outcomes of one's own actions. For instance, in a previous psychophysical experiment we demonstrated a clear correlation between the strength of delusions of influence and the ability of schizophrenia patients to cancel self-induced retinal information in motion perception (Lindner, Thier, Kircher, Haarmeier, & Leube, 2005). A number of other studies further support the hypothesis that efference copy mechanism failure may be involved in the emergence of psychotic symptoms (Daprati et al., 1997; Franck et al., 2001; Shergill, Samson, Bays, Frith, & Wolpert, 2005).

The neural correlates of disturbed efference copy mechanism in patients with schizophrenia have been less clear so far. Some new electroencephalography (EEG) studies have described an electrophysiological correlate of the efference copy mechanism using a time frequency decomposition of EEG recorded during a simple self-paced button-pressing task. They suggest that contralateral neural activity over the sensorimotor cortex that occurs before a movement is performed may reflect generation of the efference copy. Interestingly, this activity is reduced in patients with schizophrenia (Ford, Roach, Faustman, & Mathalon, 2008). In another study of this research group, altered and unaltered sensory feedback of one's own voice was compared between patients with schizophrenia and healthy controls. In controls, the N100 to unaltered self-voice feedback was dampened relative to altered self-voice or alien auditory feedback. This pattern was not seen in hallucinating patients.

The data support a connection between auditory verbal hallucinations and the imprecision of the corollary discharge heralding the sensory consequences of thoughts and actions (Heinks-Maldonado et al., 2007). These two studies suggest that patients with schizophrenia may show an impairment in efference copy mechanisms that occurs for different classes of motor actions (vocal, hand movement).

Our fMRI study extends these findings. It shows that reduced activation in the putamen, a subcortical structure that is part of the basal ganglia, may lead to a missing attenuation of sensory areas for movement perception in patients with schizophrenia. The present findings for control participants replicate our previous finding (Leube et al., 2003) that the left putamen is involved in producing the corollary discharge that is dysfunctional in patients with schizophrenia.

The thalamus also showed a higher activation in healthy controls than patients with schizophrenia during the task, irrespective of delay length. A specific role for central thalamus in higher-order aspects of visuomotor control and efference copy mechanisms has been suggested before (Bellebaum, Daum, Koch, Schwarz, & Hoffmann, 2005; Wyder, Massoglia, & Stanford, 2003). Neural models of schizophrenia have implicated the thalamus in deficits of early sensory processing and multimodal integration in many studies (Sim, Cullen, Ongur, & Heckers, 2006).

In summary we propose that the failure of efference copy mechanisms in schizophrenia may be based on a dysfunction of predictive motor mechanisms in subcortical structures. As a consequence of this dysfunction, cortical areas for movement processing may not be attenuated when patients with schizophrenia observe their own movements giving them the impression that their own movements are externally controlled. The study adds functional imaging evidence to the existing data pool that supports the assumption of a dysfunctional efference copy mechanism in schizophrenia. Future studies are needed to investigate in greater detail the interplay between different brain regions in implementing efference copy mechanisms and how these dysfunctions generate the experiences that characterize psychopathology in this disease.

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