

Case Report

FMRI in Prodromal Schizophrenia

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Abstract

We report the case of a young woman who presented with several months ongoing formal thought disorder and deterioration of social functioning. Our differential diagnosis included cognitive impairment after malaria, schizotypal disorder and prodromal schizophrenia. With a combination of clinical observation, neuropsychology and functional magnetic resonance tomography (fMRI) measurement, we were able to establish the diagnosis of prodromal schizophrenia. This diagnosis was confirmed by a short psychotic outburst two months later. The additional acquired fMRI-measurement was in line with fMRI results of a study with unmedicated schizophrenic patients. Our fMRI measurement showed hypofrontality during a bimodal attention task which was reversed by treatment with clozapine. This case report documents the transition of prodromal schizophrenia to full-blown schizophrenia with the help of neuropsychology, fMRI and psychopharmacological treatment (German J Psychiatry 2010; 13: 57-60).

Keywords: prodromal schizophrenia; fMRI; hypofrontality; clozapine; thought disorder

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Introduction

Prodromal schizophrenia has not been included in DSM-IV or ICD-10 because of difficulties in conceptualizing the broad range of unspecific symptoms. However, in some cases it provides the best diagnosis in terms of treatment and prognosis. We were able to study the course of prodromal signs until first development of full-blown psychotic signs in a patient with additional neuropsychological testing and functional magnetic resonance tomography (fMRI) measurements.

We present the case of a young woman with eccentric behavior, social isolation and formal thought disorder. The differential diagnosis included disorganized schizophrenia, cognitive impairment due to malaria, schizotypal disorder and prodromal schizophrenia. During the course of the treatment we did 2 fMRI-studies measuring bimodal passive

attention, which revealed different states of prefrontal cortex engagement in the treatment course.

The patient was a 26-year old woman who lived alone and without work in southern Germany.

She was the third daughter of a wealthy German farmer. The childhood development was unremarkable. After graduating from German college equivalent with average marks, she did a six months long journey through India. Back in Germany, she started studies in ethnology but discontinued after one year. She moved back to her parents who were afraid of the social isolation of her daughter and urged her to seek treatment. This led to great tensions between the patient and her parents. Despite her social isolation she was interested in social contacts but described some eccentric attitudes toward others which made social contact difficult. The parents reported a shy behavior during childhood, but no major loss of developmental milestones. The problems seemed to start at the age of 22 years, after having completed the Indian voyage. Relationships to men were short and superficial. Her

chief complaints were loss of self-esteem, her unsatisfying life-situation and affective lability. She showed some oddities in her beliefs and an interest in esoteric issues. The most pronounced deficit was in her formal thinking, which was circumstantial and sometimes on the border of being incoherent. Speech was generally loose, digressive and vague. Responses were far too abstract and words were sometimes used in unusual ways. Social contact was stiff and constricted. There were also tendencies in avoiding social contacts in group therapies. She was avoiding face-to-face interaction and showed peculiar mannerisms. However, she did not suffer from first-rank symptoms of schizophrenia and ICD-10 criteria for schizophrenia were clearly not fulfilled. Her symptoms were clearly distinguishable from negative symptoms in schizophrenia. Her psychiatric history was bland. We did not detect any signs for prodromal schizophrenia like adolescent depression, traumatic events, etc. She had occasionally tried cannabis and psilocybine but denied any regular drug abuse. Her somatic history showed an episode of malaria tertiana after her journey to India which had been diagnosed and successfully treated in a German hematologic unit with mefloquine 3 years before admission to our hospital.

Aripiprazole treatment did not yield any clinical improvement. After reassessment of the diagnosis, we began a two week treatment with clozapine. After one week there was a good improvement in her formal thinking, the patient was less chaotic in her everyday life, a change which was noticed by her. We stopped clozapine for two weeks for reevaluation and due to complaints of weight gain. The chaotic and eccentric behavior started to rise again. The patient was discussed in our clinical case conference where a majority of the psychiatrists did not see schizophrenia criteria fulfilled. As a consequence of this, medication was stopped and psychotherapy was continued.

After discharge to a day hospital the patient developed a short course of acoustic hallucinations and suffered from paranoid ideas of reference. This allowed for the first time the diagnosis of schizophrenia according to operational zed criteria.

Methods

We performed thorough psychopathological and neurological examinations, routine laboratory tests including cobalamin, vitamin b6 and urinary drug testing, EEG, ECG, clinical MRI and CSF testing.

Clinical Assessment was done with a SKID I and II interview. The clinical course was evaluated by two experienced psychiatric registrars. A neuropsychological work-up consisted of working memory tests and test of the executive

functions (trail-making-test, d2-Brickenkamp and Wisconsin-Card-Sorting-Test). Functional magnetic resonance imaging was done on a 1.5 T Siemens Vision scanner with echoplanar-imaging. We used a block design paradigm where patients view acoustic (pop song) and visual (moving geometric forms) stimuli both separately and together. The aim of this paradigm is to test the top-down modulation of information processing networks. The prefrontal cortex modulates higher association cortices in healthy probands. Details of the paradigm have been described in Braus et al. (2002) Preprocessing and data analysis was done with spm5 (8 mm Gaussian filter). Region-of-interest-analysis was done with WFUPickatlas. Due to the simplicity of the task, there are almost no learning effects after several measurements.

Results

SKID-Interviews did not yield a clear diagnosis. Especially schizophrenia categories were not fulfilled, with thought disorder as the only clear-cut symptom. We did not detect early prodromal schizophrenic signs like adolescent depression, traumatic events, neurological soft signs, delayed childhood development, etc. On neuropsychological examination there were pronounced difficulties in tests of the executive function. Especially the Wisconsin-Card-Sorting-Test showed high perseveration scores of 43.5 % without medication, 37.5% with aripiprazole. The following testing sessions were normal, probably due to learning effects after repeated measurements. FMRI results showed a marked contrast between an unmedicated state and following two weeks treatment with clozapine. Under medication-free conditions there was no prefrontal activity during the task which is typical for patients suffering from schizophrenia. Under treatment with 112.5 mg clozapine was a marked activation of the prefrontal cortex as it is usually encountered in healthy probands. This result is shown in figure 1.

Discussion

Prodromal schizophrenia is a difficult category. Despite several attempts to conceptualize this early stage of schizophrenia, the prognostic value of large psychometric instruments is still not convincing (Häfner 2005). Prospective studies looking for neurobiological and neuropsychological markers of prodromal schizophrenia are still missing, probably due to the difficult task of getting a large sample of people suffering from prodromal schizophrenia.

In our case the differential diagnosis of cognitive impairment due to malaria was dismissed due to the progressive course which is rather unusual in this disease. Schizotypal personality disorder did bear some resemblance, however most patients in a clinical context present with a clear first-onset psychosis.

There are several models conceptualizing early prodromal signs. How do they define the long prodromal phase seen in our patient? The first systematic German account was done by Conrad (Conrad, o. J.). His stage “trema” was described as showing depression, social withdrawal and uncertainty. In the Anglo-American context Docherty’s stage model is often discussed. His stage no. 1 is described as showing “overextension”: a phase of passivity, overstimulation, irritability and first signs of cognitive impairment (Docherty et al., 1978). The link between schizotypal disorder, prodromal signs and the cognitive impairment in schizophrenia was termed “schizotaxia”, which is a good description of our patient’s psychopathological profile (Tsuang et al. 2005)

An endophenotype would provide us with a neurobiological

marker of prodromal schizophrenia. Due to the lack of studies with prodromal schizophrenia, we must draw from other studies from the schizotypic spectrum.

From sustained attention deficits have been posited as a potential endophenotypic marker of vulnerability to schizotypia (Raine et al. 2002). Our case report evaluates attentional deficits in the treatment course by clinical observation, neuropsychological testing and a crossmodal attention pharmacofMRI paradigm.

fMRI is still far away from being integrated in a clinical context as a diagnostic tool. However, in a difficult diagnosis of thought disorder an fMRI-task designed for showing schizophrenic hypofrontality added valuable data to clinical observation and neuropsychological testing.

Our main finding is the correlation of prefrontal activation in a crossmodal attention task due to clozapine treatment in schizotypal disorder. Without clozapine, prefrontal activation wasn't detectable, with clozapine it was normalized to the levels of healthy subjects. Prefrontal dysfunction is a key concept in schizophrenia and was tested in other disorders

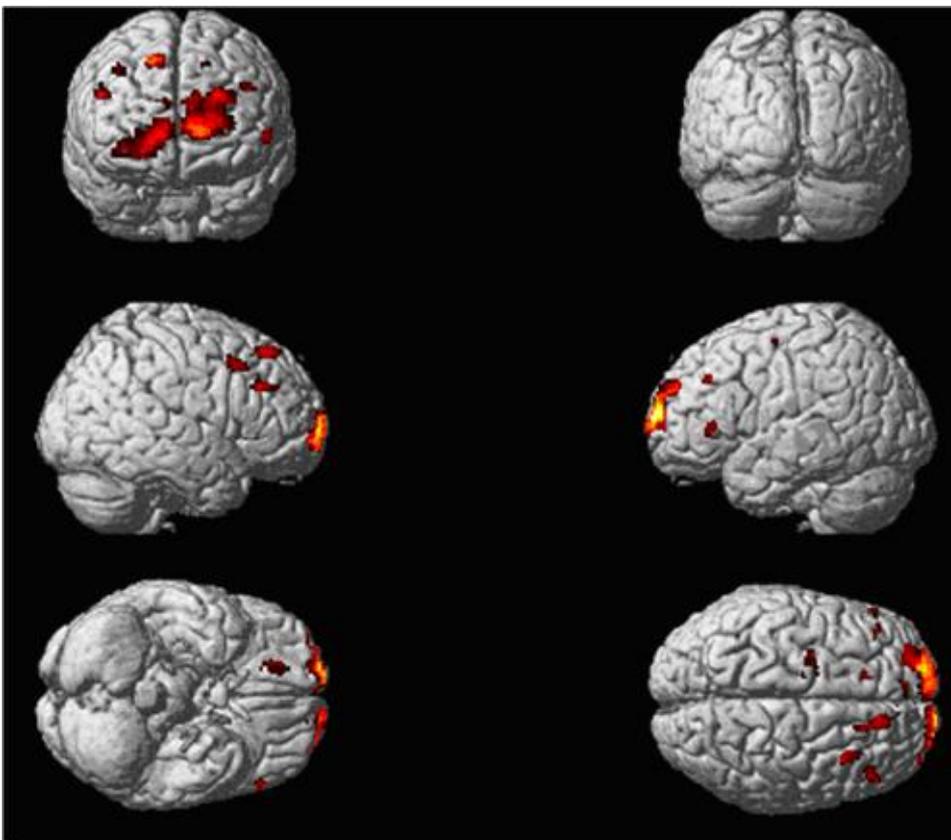


Figure 1. The contrast highlights where cortical activity was higher after the patient received clozapine compared to no medication ($p < 0.001$, uncorrected). After clozapine treatment, the BOLD response is much higher in the highlighted areas of the prefrontal cortex.

of the schizotypic spectrum as well. Our fMRI task showed a prefrontal activation during crossmodal visual and auditory stimuli, a finding which is in good correlation with closely related studies. The dorsolateral cortex is a key hub in a network mediating attention to sensory stimuli (Shomstein & Yantis, 2004). Dopamine is a key modulator of the signal-to-noise ratio in information processing. Our own fMRI-task is a direct measure of sensoric information processing and proved to be sensible for detecting cognitive improvement by clozapine. Neuropsychological profiles in schizotypal disorder show cognitive deficits especially in executive functions and attention mediated by the dorsolateral cortex. Our own result is compatible with neuroimaging studies which underscore the importance of a prefrontal dysregulation in schizophrenia and related disorders (Heinz et al., 2003). However, up to now, there are no studies in prodromal schizophrenia. Our case is a hint for the usefulness of the hypofrontality concept in establishing a diagnosis in prodromal schizophrenia.

Furthermore, our case underlines the usefulness of clozapine for thought disorder in prodromal schizophrenia. Clozapine is a potent modulator of prefrontal dopamine, providing a direct intervention for the disturbed prefrontal activity. A general treatment of prodromal schizophrenia – especially with clozapine - might provide an ethical dilemma for psychiatrists because of unnecessary treatment with severe side effects. Additional diagnostic tools like fMRI could help to distinguish these patients who benefit from an early pharmacological treatment.

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