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Neurocognitive functioning in parents of schizophrenia patients: Attentional and executive performance vary with genetic loading

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ABSTRACT

Neuropsychological deficits are candidate endophenotypes of schizophrenia which can assist to explain the neurocognitive impact of genetic risk variants. The identification of endophenotypes is often based on the familiality of these phenotypes. Several studies demonstrate neuropsychological deficits in unaffected biological relatives of schizophrenia patients without differentiating between genetic and non-genetic factors underlying these deficits. We assessed $N=129$ unaffected biological parents of schizophrenia patients, $N=28$ schizophrenia patients (paranoid subtype), and $N=143$ controls without a family history of schizophrenia with an extensive neuropsychological test battery. Direct comparison of $N=22$ parents with an ancestral history of schizophrenia (more likely carriers, MLC) and $N=17$ of their spouses without such a history (less likely carriers, LLC) allowed the separation of genetic and non-genetic aspects in cognition. Overall, parents showed significant deficits in neuropsychological tasks from all cognitive domains with medium effect sizes. Direct comparisons of MLC- and LLC-parents showed that attentional and executive tasks were most strongly affected by genetic loading. To conclude, unaffected parents of schizophrenia patients showed modest yet significant impairments in attention, memory, and executive functioning. In particular, attentional and executive impairments varied most strongly with genetic loading for schizophrenia, prioritising these dysfunctions for genotype-endophenotype analyses.

1. Introduction

Schizophrenia is a clinically heterogeneous and aetiologically complex disorder affecting approximately 1% of the population worldwide (Messias et al., 2007). Genetic variation plays a significant role in the aetiology of schizophrenia as indicated by family, twin, and adoption studies (e.g. Sullivan et al., 2003). However, only a small proportion of variance is explained by potential candidate variants identified to date.

The identification of schizophrenia susceptibility genes by using the disease phenotype has proven to be difficult. The pathogenesis of schizophrenia is highly complex resulting in just a weak predictive relationship between clinical diagnosis and underlying genotype (e.g. Owen, 2012). The concept of endophenotypes provides a possible solution to this difficulty. Endophenotypes or intermediate phenotypes are markers of risk for the illness. They are considered to have “a simpler genetic architecture” than the disorder itself and therefore may be used to bridge the gap between clinical phenotype and genotype (Gottesman and Gould, 2003; Braff et al., 2007; Glahn et al., 2014). Thus, validated endophenotypes may provide a tool to directly identify genes conferring risk for schizophrenia. With the invention of modern genetic analyses techniques such as large scale genome wide analyses and next generation sequencing techniques, a second and particularly valuable feature of endophenotypes may lie in their ability to provide insight into the functional effects of e.g. a genome wide significant variant on brain functions (Flint et al., 2014).

Neurocognitive deficits are one of the core features of schizophrenia (Kalkstein et al., 2010). This raises them to potential

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candidates for endophenotype research on this disorder. Schizophrenia patients show neuropsychological deficits in a variety of cognitive test measures. Numerous studies and meta-analyses provide evidence for a global cognitive impairment with emphasis on attention, declarative memory, and executive functioning (Dickinson et al., 2007; Schaefer et al., 2013).

To be considered suitable as endophenotypes, these deficits should as well be present in clinically unaffected biological relatives of patients (Gottesman and Gould, 2003). Studies on cognition in biological relatives of schizophrenia patients are less consistent than those in patients, but most studies that investigated neuropsychological differences between relatives and controls report dysfunctions in relatives as well. Biological relatives, even though not clinically affected, also show impairments on a wide array of cognitive tasks, albeit to a lesser degree than schizophrenia patients (Sitskoorn et al., 2004; Snitz et al., 2006). Snitz et al. (2006) published a meta-analytic review on the literature on cognitive deficits of unaffected first-degree relatives of schizophrenia patients comprising 58 studies. They report mean effect sizes in the small to moderate range ($d=0.00$–0.68), with the largest difference for category fluency (Snitz et al., 2006).

Up to now only a small number of studies have focused on parents of schizophrenia patients. Studying parents of schizophrenia patients has two important advantages over studying their children or siblings as first-degree relatives. First, parents of patients have almost completely passed through the age of risk for developing schizophrenia. Therefore, deficits in parents are very unlikely to result from a clinically silent, prodromal state of schizophrenia-something which cannot be excluded in children and siblings. Second, if there is a positive family history for schizophrenia in one (but not the other) parental ancestry, it can be assumed that this parent of a patient carries (more) genetic variation conferring risk for schizophrenia, as compared to her or his spouse. Such a difference in genetic load cannot be inferred in children or siblings of affected individuals, at least not without tracing their future offspring. Therefore, we studied biological parents of patients with schizophrenia in order to (1) delineate endophenotypic deficits independent of possible prodromal deficits, and (2) to examine which endophenotype measures would be most sensitive to the assumed variation of genetic load.

Comparing parents differing in their genetic liability for schizophrenia as determined by their ancestry may be especially informative for the endophenotype approach as it allows approaching the tricky issue of separating genetic from non-genetic influences. To our knowledge, only one study investigated neuropsychological deficits in positive-history parents for schizophrenia so far. Harris et al. (1996) examined aspects of attention, learning and memory (but not executive functioning) in 14 schizophrenia patients, 28 parents (eight of them classified as positive and eight as negative-history parents) and 18 controls (Harris et al., 1996). Comparisons of patients and parents showed that patients significantly differed from the negative-history parents but not from the positive-history parents on an aggregate index of attention. The authors conclude that a dysfunction in attention is the primary heritable component of the neuropsychological deficit in schizophrenia. However, Harris et al. (1996) did not report direct comparisons of positive- and negative-history parents.

The aim of the present study was to address this issue. We recruited a large sample of clinically unaffected parents of schizophrenia patients, grouped them by ancestral history and employed a comprehensive neuropsychological test battery. Direct comparisons of positive- and negative-history parents embedded in a large parent-control-study allowed the identification of neuropsychological core endophenotypes thus helping to resolve the ongoing controversy on this issue.

2. Methods

2.1. Subjects

The sample consisted of 129 non-affected biological parents of schizophrenia patients, 22 of them classified as positive- and 17 as negative-history-parents (see below), 28 patients with schizophrenia (not related to the parent sample), and 143 healthy control subjects. All subjects were interviewed with the German version of the Structured Clinical Interview for DSM-IV axis I and axis II for psychiatric diagnoses (SCID-I and SCID-II) (Wittchen et al., 1997). Exclusion criteria (symmetric for all probands) were: a history of neurological illness or another severe medical condition that might alter neurocognitive functioning, head injury with loss of consciousness for more than 5 min or with neurocognitive sequel, mental retardation, substance abuse in the past six months or lifetime history of substance dependence, and intake of psychiatric or other medications that act on the CNS in the past six months (not applied to the patient group).

All participants gave their written informed consent prior to inclusion into the study. The study was approved by the local ethics committees and was conducted in accordance with the Helsinki Declaration.

Studied patients ($n=28$) were consecutive admissions to the Psychiatric University Hospitals of Bonn and Cologne (Germany). Schizophrenia diagnosis according to the DSM-IV criteria was assured by the SCID interview. The sample consisted of 20 men and 8 women, the average age was 30 years (range: 17–45) (see Table 2). All patients were assigned to the paranoid subtype based on lifetime symptom presentation although temporary negative and disorganised symptoms were also present in most cases.

Parents of schizophrenia patients were recruited after written consent of schizophrenia index-patients from five psychiatric hospitals of Bonn and Cologne. Additional exclusion criterion for parents was a lifetime diagnosis of any psychotic disorder. Each parent was interviewed by a trained clinical psychologist or psychiatrist using an in-depth-interview, the SCID-I and the Family Informant Schedule and Criteria (FISC) to obtain psychiatric family histories and to construct genograms (Mannuzza et al., 1985). If available, medical records were obtained additionally. All collected information about the parents' families was evaluated by a senior psychiatrist (S.R. and J.D.) and the interviewer to establish best-estimate diagnoses for all relatives (first, second, and third degree) of the parents. A total of 129 biological parents without a lifetime history of any psychotic disorder (DSM-IV) were included. The parent sample consisted of 45 fathers and 84 mothers with a mean age of 58 years (range: 41–80) (see Table 2).

A more likely carrier (MLC) was defined as a non-affected biological parent of a schizophrenic child who has at least one more affected relative in his or her family pedigree (first, second or third degree ancestor) with a lifetime history of DSM-IV schizophrenia. A less likely carrier (LLC) was defined as a non-affected biological parent of a schizophrenic child who has no further affected relative in his family pedigree (up to third degree) and whose spouse has been classified as MLC. The remaining 90 parents had no known or no clearly diagnosable further affected relative in their family pedigree (apart from their affected child) and no spouse with a definite positive family history.

Control participants ($N=143$) were recruited on the basis of a random selection from community registers in Bonn and Cologne. Selection criteria were the same as for patients and relatives. Additional requirement was no personal or family history of DSM-IV psychotic disorder (up to the third degree of kinship). Other psychiatric diagnoses were allowed. We used symmetric exclusion criteria to avoid the recruitment of “supernormal” controls. In total, $N=143$ control subjects participated, of whom $N=36$ and

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