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Secondary verbal memory: a potential endophenotype of schizophrenia

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Abstract

This study aimed at identifying neuropsychological endophenotypes of schizophrenia which met the criteria of stability and sensitivity. Twenty-six non-schizophrenic first-degree relatives together with their affected family members (all simplex-families) underwent assessment with a comprehensive neuropsychological test battery both at baseline and 13 months follow-up. Follow-up patients were in a state of stable remission. Further, 21 unrelated, demographically balanced, non-vulnerable controls were tested one at a time. A principal components analysis of our test battery resulted in four factors: (1) Vigilance, attention, and psychomotor, (2) secondary verbal memory, (3) immediate and working memory, and (3) abstraction and problem solving. At baseline testing our study revealed a pattern of selective cognitive deficits in the relative group that is less pronounced, yet qualitatively similar, to that found in the patient sample. The most severe deficits displayed both the patients and their relatives in the secondary verbal memory domain. The dysfunctions in secondary verbal memory at baseline testing significantly correlated with negative symptoms only. Secondary verbal memory deficits proved to be relatively independent of age at onset of illness, illness duration, and neuroleptic dosage. Longitudinally, dysfunctions in the patients' secondary verbal memory fluctuated over time and with negative symptoms, and persisted in remitted patients at the same level as in their relatives. In conclusion, the secondary verbal memory met the criteria of relative stability and sensitivity in our sample of simplex-families. Thus, the secondary verbal memory seems to be a potential endophenotypic marker of schizophrenia, even for cases with a hypothetically lower genetic loading.

Keywords: Schizophrenia; Neuropsychology; Secondary verbal memory; Endophenotypes; First-degree relatives of schizophrenics; Genetic loading

1. Introduction

Enormous evidence exists that schizophrenia is accompanied by severe cognitive deficits in attention, memory, and executive functions (Goldberg and Gold, 1995; Heinrichs and Zakzanis, 1998 for reviews). However, little is known if such dysfunctions occur as a consequence of the disease or are etiologically relevant and thus might serve as biobehavioral markers of a genetic vulnerability to schizophrenia (Tsuang et al., 1993). One approach to resolving this question is the neuropsychological examination of the non-psychotic, first-degree relatives of schizophrenic patients (Kendler and Diehl, 1993). Unlike studies of schizophrenic patients, studies of their relatives are not confounded by neuroleptic medication, psychopathology or potentially neurotoxic chronic illness processes. Previous studies reported that the relatives of patients with schizophrenia exhibit dysfunctions in executive functioning, verbal memory, attention and verbal ability (Cannon et al., 1994; Keefe et al., 1994; Faraone et al., 1995). In summary, such studies revealed a pattern of deficits that is milder, yet qualitatively similar to those found in schizophrenic patients themselves (Kremen et al., 1994 for review). However, all of these studies tested the relatives just once in time. Thus, we cannot yet consider these neuropsychological deficits to be putative endophenotypic markers, a term referring to characteristics that are thought to be causally closer to the pathogenic genotype than the clinical phenotype itself (Gottesman et al., 1987; Gottesman, 1991; Kremen et al., 1998).

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To qualify such neuropsychological dysfunctions as endophenotypes, the variable under study has to meet three criteria (Kremen et al., 1994). First, it has to be present and relatively stable in schizophrenic patients (stability). Second, it should be demonstrable over time in those individuals being at risk for schizophrenia, i.e. in relatives (sensitivity). And third, it has to be less common in patients with other psychiatric disorders (specificity). In addition, biobehavioral markers that reflect a genetic liability to schizophrenia should be relatively independent of acute psychotic symptoms, and clinical variables like age at onset of illness or illness duration. Variables of the neuroleptic medication like current daily dosage, lifetime duration of neuroleptic treatment, and different influences of typical and atypical neuroleptics on neuropsychological performance are also discussed as potential confounders (Albus et al., 2002). So far, there is also conflicting evidence of a relationship between changes in psychopathology and cognitive functioning over time (Censits et al., 1997; Hughes et al., 2002).

To identify sensitive markers of a genetic vulnerability to schizophrenia it is essential to investigate further the stability of the neuropsychological dysfunctions found in relatives of schizophrenic patients. To date, only one study (Faraone et al., 1999) has been published that tested the hypothesis that the neuropsychological dysfunctions among the relatives of schizophrenic patients are stable over time.

To summarize, our study is aimed at identifying neuropsychological endophenotypes which fully meet the criteria of stability and sensitivity. A proper examination of these criteria requires schizophrenics to be assessed as well as their non-affected first-degree relatives both at baseline and follow-up. So far, there is no study that has neuropsychologically examined entire "schizophrenic" families over time. We used this more sophisticated combined cross-sectional and longitudinal design to test the following hypotheses: (1) relatives of schizophrenic patients present a qualitatively similar but milder profile of neuropsychological deficiencies than the affected individuals themselves, and (2) relatives exhibit stable neuropsychological dysfunctions. Furthermore, this design allows examining the course of the patients' neuropsychological functions. Two competing empirical findings exist: (1) cognitive deficits do not appear to deteriorate over time, but rather to represent a static encephalopathy (Hoff et al., 1992, 1999; for review: Goldberg et al., 1993; Rund, 1998), and (2) considerable improvement in neuropsychological functioning can occur after sustained recovery had been achieved (Sweeney et al., 1991; Bilder et al., 1991; Nopoulos et al., 1994; Rund and Landrø, 1995). One open question regarding the latter finding relates to possibly confounding practice effects.

Other foci of this study are not only cross-sectional but also longitudinal correlation analyses to examine the relationship between neuropsychological functioning and potential confounders like psychopathology, age at onset of illness, illness duration, and neuroleptic medication.

2. Methods

2.1. Subjects

2.1.1. Selection analysis

Between July 1999 and June 2001, 44 inpatients who met DSM-IV criteria for schizophrenia or schizoaffective disorder were consecutively recruited as part of a combined large-scale psychotherapy and neuropsychology study at the University Hospital for Psychiatry and Psychotherapy, Tuebingen, Germany. Diagnoses were determined by the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen et al., 1997). All patients gave written informed consent to participate in the study, which was approved positively by the local ethics committee. Patients were selected on the basis of the following inclusion criteria: (1) stabilization phase of illness, and (2) ages between 18 and 60 years. Exclusion criteria for neuropsychological testing were as follows: (1) lifetime history of substance dependence or substance abuse (DSM-IV/SCID-I) during the last month before recruitment, (2) neurologic disease or damage, (3) medical illnesses that may interfere with cognitive function, (4) history of head injury with loss of consciousness greater than 5 min, (5) mental retardation (IQ below 80 according to the MWT-B (Lehrl, 1992), a German vocabulary test measuring the premorbid intellectual level), and (6) insufficient German language skills. Thirty-eight out of the 44 patients agreed to neuropsychological testing.

These 38 patients had a total of 115 first-degree relatives (66 parents, 37 siblings, and 12 offspring). Eighty-nine relatives from 23 patients could not be included in the study for the following reasons. For the neuropsychological examination first-degree relatives had to fulfill the following inclusion criteria: (1) no history of psychotic or affective disorders (DSM-IV/SCID-I), (2) currently no taking of psychotropic medications, and (3) ages between 16 and 69. Exclusion criteria for relatives were in correspondence with patients'. Relatives were screened by the author (AW) to determine eligibility and ascertain informed consent to testing. Of the 115 relatives 29 (25.2%) had to be excluded for the following reasons: (1) twenty-four were younger than 16 years or older than 69 years, (2) two had severe psychiatric disorders (schizophrenia and bulimia nervosa with hospitalization at time of study), (3) one suffered from serious medical illness, and (4) two presented insufficient