Anhedonia in schizophrenia: a distinct familial subtype?

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Abstract

Failures to replicate results in psychiatric genetics might be due to our inability to define the heritable phenotype. Instead of relying entirely on classical nosographical approaches, the use of a candidate symptom approach to identify more homogeneous forms of diseases among affected subjects and subclinical traits among first-degree relatives may increase genetic validity. Anhedonia may be a marker for subjects at risk of schizophrenia or schizophrenia spectrum disorders. We compared the familiality of anhedonia characterized by a high level of physical anhedonia (score above 23) in a sample of schizophrenic probands ($N = 80$) and their relatives ($N = 78$), with that in bipolar patients ($N = 109$), their relatives ($N = 33$) and normal controls ($N = 94$). We identified a subform of schizophrenia characterized by highly anhedonic schizophrenic probands with a three-fold higher familial risk of schizophrenia and schizophrenic spectrum disorders. We also found that their first-degree relatives had a high level of anhedonia. An intrafamilial correlation analysis confirmed the familial nature of anhedonia. Our data suggest that anhedonia is a candidate symptom for schizophrenia. Refining phenotype definition by studying subgroups of anhedonic and non-anhedonic probands with relevant candidate genes might be fruitful.
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1. Introduction

Obstacles to the identification of genes underlying genetic vulnerability to schizophrenic disorders are largely associated with our inability to define the heritable phenotype (Tsuang, 1993; Leboyer et al., 1998). Although reliable diagnostic criteria have been used in psychiatric genetics, little is known about how to choose the diagnostic system that best describes the most heritable form of the illness. Among apparently affected subjects, various types of phenotypic misclassification reduce the power of linkage and association studies because of phenocopies or genetic heterogeneity. Furthermore, the risk of schizophrenia in the offspring of unaffected monozygotic twins of schizophrenic subjects is similar to that of the offspring of their schizophrenic cotwins. Thus, unaffected subjects carrying vulnerability genotypes are not identified

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by the classical nosographical approaches (Gottesman and Bertelsen, 1989). Our inability to identify apparently unaffected subjects or controls that carry vulnerability genes, due to incomplete penetrance, also reduces the power of genetic studies.

To minimize the arbitrariness of categorical diagnoses, new strategies have been developed to define phenotypes as subclinical quantitative traits called endophenotypes (Leboyer et al., 1998). Quantitative measures provide more power in linkage analyses than categorical diagnosis (Carey and Williamson, 1991). Furthermore, endophenotypes might be valuable for identifying common alleles with nonspecific and moderate effects on disease risk (Tsuang, 1993). Endophenotypes are biobehavioral traits, also called intermediate phenotypes or simply covariates, which correlate with the main trait of interest and can be used to define the trait or its underlying genetic mechanism more accurately (Ott, 1995). The first step in identifying a potential vulnerability marker is to demonstrate that a trait is more frequent in relatives of schizophrenic individuals than in relatives of controls. For example, it has been suggested that anhedonia, defined as the loss of the capacity to feel pleasure (Ribot, 1897; Myerson, 1922), is a marker for subjects at risk of schizophrenia or schizophrenia spectrum disorders (i.e. schizophrenia, schizo-affective disorders, schizophreniform trouble, schizotypal, schizoid and paranoid personality disorders) (Chapman and Chapman, 1984). Anhedonia can be measured by a series of scales developed by Chapman et al. (1976), including the Physical Anhedonia Scale (PAS) and the Social Anhedonia Scale (SAS) (Mishlove and Chapman, 1985). A greater heritability has been found for the Physical Anhedonia Scale than for the Social Anhedonia Scale (Lyons et al., 1995; Clementz et al., 1991; Berenbaum and McGrew, 1993). It has been demonstrated that anhedonia is a specific dimension, which is distinct and separate from depression and schizophrenic symptomatology, in chronic schizophrenia (Loas et al., 2000). Anhedonia is also a stable trait in schizophrenic patients (Keefe et al., 1991; Rey et al., 1994; Dollfus and Petit, 1995).

Using a family design, seven studies have used the Chapman self-report questionnaire of physical anhedonia (Chapman et al., 1976) to assess anhedonia among relatives of schizophrenic probands and among relatives of controls. Five of these reports found that anhedonia was significantly more common among relatives of schizophrenics (Katsanis et al., 1990; Clementz et al., 1991; Grove et al., 1991; Franke et al., 1993; Kendler et al., 1996), whereas two did not (Erlenmeyer-Kimling et al., 1993; Craver and Pogue-Geile, 1999). This disagreement might be explained by methodological problems such as the inclusion of heterogeneous groups of patients (schizophrenia and/or first psychotic episode and/or major depression with psychotic features and/or bipolar mania with psychotic features), nonsystematic lifetime assessment of psychiatric disorders using structured interviews, inclusion of affected subjects among relatives, inclusion of normal controls who might be carriers of vulnerability factors (controls below the age at onset of the disorder studied, presence of a positive psychiatric family history that was not systematically assessed), absence of a contrasted psychiatric control group and differences in the procedures used to measure anhedonia (Social Anhedonia Scale or Physical Anhedonia Scale).

In this study, after lifetime diagnostic assessment, we compared anhedonia as measured by Physical Anhedonia Scale (PAS) scores, in schizophrenic patients, bipolar patients, their respective nonschizophrenic or non-bipolar first-degree relatives, and healthy controls. The aim was to determine whether anhedonia is familial, i.e. more prevalent among nonschizophrenic relatives of schizophrenic probands or only among relatives of a subgroup of anhedonic schizophrenic probands. We also aimed to determined if a high anhedonia score in schizophrenic probands is associated with an increased risk for schizophrenia or schizophrenia spectrum disorders in relatives.

2. Materials and methods

2.1. Subjects

Probands suffering from bipolar disorders or schizophrenia were recruited from consecutive admissions to Pitié-Salpétrière or Albert Chenevier Hospitals (Paris). They were included in the study just before discharge. Patients had to meet the DSM-IV criteria for bipolar disorder or schizophrenia disorder (American Psychiatric Association., 1994). To confirm the diagnosis of either bipolar disorder or schizophrenia among probands, patients were directly interviewed