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Dissecting the catatonia phenotype in psychotic and mood disorders on the basis of familial-genetic factors

Victor Peralta [a,b,*], Lourdes Fañanás [c,d], Migdyrai Martín-Reyes [a,b], Manuel J. Cuesta [b,e]

[a] Mental Health Department, Servicio Navarro de Salud, Spain
[b] Instituto de Investigación Sanitaria de Navarra (IdiSNa), Spain
[c] Unitat d' Antropologia, Department of Biology Animal, Facultat de Biologia, Universitat de Barcelona, Spain
[d] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain
[e] Psychiatry Service, Complejo Hospitalario de Navarra, Spain

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ABSTRACT

Background: This study examines the familial aggregation (familiality) of different phenotypic definitions of catatonia in a sample of multiplex families with psychotic and mood disorders.
Methods: Participants were probands with a lifetime diagnosis of a DSM-IV functional psychotic disorder, their parents and at least one first-degree relative with a psychotic disorder. The study sample included 441 families comprising 2703 subjects, of whom 1094 were affected and 1609 unaffected. Familiality (h^2) was estimated by linear mixed models using family membership as a random effect, with h^2 indicating the portion of phenotypic variance accounted for by family membership.
Results: Familiality estimates highly varied for individual catatonia signs ($h^2 = 0.17–0.65$), principal component analysis-derived factors ($h^2 = 0.29–0.49$), number of catatonia signs present ($h^2 = 0.03–0.43$) and severity of the catatonia syndrome ($h^2 = 0.25–0.59$). Phenotypes maximizing familiality estimates included individual signs (mutism and rigidity, both $h^2 = 0.65$), presence of ≥5 catatonia signs ($h^2 = 0.43$), a classical catatonia factor ($h^2 = 0.49$), a DSM-IV catatonia syndrome at a severity level of moderate or higher ($h^2 = 0.59$) and the diagnostic construct of psychosis with prominent catatonia features ($h^2 = 0.56$). Familiality estimates of a DSM-IV catatonia syndrome did not significantly differ across the diagnostic categories of psychotic and mood disorders ($h^2 = 0.40–0.47$).
Conclusions: The way in which catatonia is defined has a strong impact on familiality estimates with some catatonia phenotypes exhibiting substantial familial aggregation, which may inform about the most adequate phenotypes for molecular studies. From a familial-genetic perspective, the catatonia phenotype in psychotic and mood disorders has a transdiagnostic character.

1. Introduction

Family-genetic factors have traditionally been regarded as a cornerstone of psychiatric nosology (Robins and Guze, 1970; Craddock et al., 2009), and there is a substantial genetic contribution to the etiology of psychotic and mood disorders (Cardno et al., 1999; Lichtenstein et al., 2009; Wray and Gottesman, 2012); however, authors disagree about the phenotype(s) definition(s) that best correlate with the familial-genetic underpinnings of psychotic disorders. A recent review of the evidence using a range of validating criteria including familial-genetic risk factors concluded that there is insufficient evidence of the etiology and pathophysiology to base classification of psychotic disorders on causality (Carpenter et al., 2009). A major research challenge is, therefore, to detect phenotypes that maximize the phenotype-genotype correlation as a first step in unravelling the molecular genetic underpinnings of psychotic disorders.

Catatonia is increasingly recognized as one of the major psychopathological domains within psychotic and mood disorders (Peralta and Cuesta, 2001a; Ungvary et al., 2010), although with a disputed nosological status regarding categories of psychiatric disorders (Pfuhlmann and Stöber, 2001; Peralta et al., 2001; Fink et al., 2010). In fact, until DSM-5, catatonia has been mainly viewed as a subtype of schizophrenia, and currently as an unspecific syndrome that may appear in many psychiatric disorders and other medical conditions (APA, 2013; Tandon et al., 2013; Braff et al., 2013). Despite the relevance of catatonia in psychotic disorders, its etiological underpinnings remains poorly researched.

Abbreviations: APA, American Psychiatric Association; CASH, Comprehensive Assessment of Symptoms and History schedule; PCA, Principal Component Analysis.

* Corresponding author at: Mental Health Department, Servicio Navarro de Salud, Plaza de la Paz s/n, 31002 Pamplona, Spain.
E-mail address: victor.peralta.martin@cfnavarra.es (V. Peralta).

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Regarding familial-genetic factors, several lines of evidence indicate that they are of importance in catatonia. First, catatonic schizophrenia appears to have higher familial loading of psychotic disorders than noncatatonic schizophrenia (Scharfetter and Nüsperli, 1980; Mimica et al., 2001; Stöber, 2004). Second, a catatonia syndrome predicts higher morbidity risk of mood disorders in the first-degree relatives of probands with psychotic disorders (Van Os et al., 1997; Peralta and Cuesta, 2007). Thirdly, the Wernicke-Kleist-Leonhard school of psychiatry (Ungvari, 1993) views catatonia as an heterogeneous syndrome from the familial-genetic perspective, in that systematic catatonia and motility psychosis exhibit low familiality, whereas periodic catatonia is highly familial (Leonhard, 1957; Franzek and Beckmann, 1998) with a morbidity risk of 26.9% and major gene effect and anticipation (Stöber et al., 1995). According to this data, catatonia appears to be a heterogeneous syndrome regarding familial-genetic risk factors, and thus a major research challenge is to detect catatonia phenotypes that maximize the phenotype-genotype correlation as a first step in unravelling their molecular genetic underpinnings.

A useful approach to this endeavour is to examine different catatonia phenotypes and compare their predictive validity regarding familial aggregation. The main goal of the present study was to examine the degree of familial aggregation, also known as familiality/transmissibility (Kendler and Neale, 2009) or multifactorial/generalized heritability (Rice, 2008), of the catatonia phenotype in a broad sample of multiplex families with psychotic and mood disorders. More specifically, we examined the familiality of (1) individual catatonia signs, (2) empirically-derived catatonia syndromes, (3) different severity definitions of a catatonia syndrome, and (4) the familiality of catatonia across diagnostic classes of psychotic and mood disorders. With these goals in mind we sought to determine the catatonia phenotype that could maximize the phenotype-genotype correlation.

2. Methods

2.1. Subjects

The methodology, including ascertainment procedure and characteristics of the subjects included in this study, has been described in detail elsewhere (Peralta et al., 2016). Briefly, probands were identified through the psychiatric case register of Navarra (Spain) as patients who had attended mental health services from a defined catchment area between 1990 and 2014. Inclusion criteria for the probands included: age >15 years, residing in Navarra, meeting a lifetime DSM-IV diagnosis for a functional psychotic disorder (APA, 1994), having at least one first-degree relative with the same diagnosis and willing to participate, as well as both biological parents being willing and able to participate. The latter criterion was required to delineate the relationships between the affected members of each family (McGrath et al., 2009). The project was approved by the ethics committee of the Regional Health Service of Navarra and written informed consent was obtained from all study participants or their legal representatives.

The present study is based on a total of 441 families comprising 2703 individuals, of whom 1094 were affected and 1609 unaffected (Table 1). The average of subjects per family was 6.98 (s.d. = 2.56, range 3–17) and the average of affected subjects per family was 2.80 (s.d. = 1.18; range 2–8). Probands and affected relatives did not significantly differ in their DSM-IV diagnoses excepting for delusional disorder (probands = 2.3%, relatives = 7.4%, $p < 0.001$); however, differences in that diagnosis, were irrelevant for this study, since, by definition, a diagnosis of catatonia is incompatible with a diagnosis of delusional disorder.

2.2. Assessment

All participants underwent face-to-face psychiatric assessments using the Comprehensive Assessment of Symptoms and History (CASH) schedule (Andreasen et al., 1992). The CASH is a semi-structured interview designed to provide a comprehensive information base concerning clinical features of psychotic and mood disorders. Because the information base is broad, the schedule is not wedded to a specific diagnostic system thus permitting clinicians and researchers to make diagnoses using a wide range of systems, including the DSM-IV classification.

Table 1
Sample description (N = 2703).

	Affected (n = 1094)	Unaffected (n = 1609)
Age, mean (s.d.), years	44.1 (15.2)	46.8 (17.3)
Gender, male, n (%)	552 (50.5)	829 (51.5)
Education, mean (s.d.), years	9.7 (3.5)	10.1 (3.1)
No. of family members affected, mean (s.d.)	2.95 (1.31)	–
No. of family members affected included in the study, mean (s.d.)	2.80 (1.18)	–
Age at illness onset, mean (s.d.), years	27.6 (11.5)	–
Time from onset, mean (SD), years	16.5 (12.2)	–
Global assessment of functioning	63.2 (21.1)	–
DM-IV diagnosis, n (%)		
Schizophrenia	395 (36.1)	–
Nonschizophrenic nonaffective psychoses	294 (26.9)	–
Bipolar disorder	239 (21.8)	–
Major depressive disorder	166 (15.2)	–

Interviews were conducted by experienced psychiatrists or clinical psychologists with established reliability (>0.80) for CASH global symptom ratings and diagnoses (Peralta et al., 2013). Full blind assessment within families was not possible, since not all family members could be assessed by different raters. Information for rating symptoms and diagnoses was derived from all available sources of information, including direct diagnostic interviews, family history reports, medical records and information provided by close relatives or significant others. Two senior researchers (VP, MJC) through a best estimate procedure using all the available records arrived at independent diagnoses, reached a consensus and determined the final diagnoses. Final diagnoses were blind performed to subject identity and group status (proband, relative) in about 75% of the pedigrees.

2.3. Definition of the catatonia phenotype

Catatonia signs were assessed by means of the catatonia module from the CASH, which includes 6 motor signs: stupor, rigidity, waxy flexibility, excitement, posturing and mannerisms, the last two items being collapsed into a single rating, and a global severity rating of catatonia. In order to achieve both a more comprehensive assessment of the catatonia syndrome and a DSM-IV diagnosis of catatonia, CASH motor signs were supplemented with 2 motor behavior items from other CASH modules (ritualistic/stereotyped behavior and motor retardation) and 3 additional catatonia items necessary to make a DSM-IV diagnosis of catatonia (negativism, mutism and echo-phenomena), which were rated according to the Modified Rogers Scale (Lund et al., 1991). A total of 10 catatonia signs were rated as their worst on a lifetime basis following the general CASH symptom scoring that combines frequency and severity and ranges between 0 (absent) and 5 (severe). A motor sign was considered to be present if it was rated at the level of mild or higher (score ≥ 2), and the total number of catatonia signs present was also recorded.

A diagnosis of catatonia was made according to the DSM-IV criteria, which was also rated according to the following severity criteria: 0 = absent catatonia signs, 1 = subclinical catatonia (catatonia signs present but not fulfilling the criteria for a catatonia diagnosis), 2 = catatonia present with mild intensity, 3 = catatonia present with moderate intensity, and 4 = catatonia present with severe intensity. A high convergent validity between the CASH and DSM-IV catatonia severity ratings has been shown (r = 0.89) (Peralta et al., 2010). We defined also a catatonia phenotype on the basis of the factor structure of the catatonia signs (see below). Lastly, and in order to achieve a phenotype definition of catatonia that takes into account the lifetime severity of the whole clinical

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