No evidence for physical anhedonia as a candidate symptom or an endophenotype in bipolar affective disorder.

Bruno Etain, Isabelle Roy, Chantal Henry, Angela Rousseva, Franck Schurhoff, Marion Leboyer, Frank Bellivier

No evidence for physical anhedonia being a candidate symptom or an endophenotype in bipolar affective disorder.

Bruno ETAIN, MD [1,2], Isabelle ROY, MD [1,2], Chantal HENRY, MD, PhD [3], Angela ROUSSEVA, MD [1,2], Franck SCHURHOFF, MD [1,2], Marion LEBOYER, MD, PhD [1,2], Frank BELLIVIER, MD, PhD [1,2].

1. AP-HP, Hopital Albert Chenevier, Département Hospitalo-universitaire de Psychiatrie ; Université Paris XII ; 94010 Créteil ; France
2. INSERM U513, Faculté de Médecine, 94000 Créteil, France
3. Service de Psychiatrie Adulte, Hôpital Charles Perrens, 33000 Bordeaux, France

Corresponding author:
Bruno ETAIN, MD
Département Hospitalo-universitaire de Psychiatrie
Hôpital Albert Chenevier
40, rue de Mesly
94010 CRETEIL cedex, France
Tel: 33 1 49 81 32 90
Fax: 33 1 49 81 30 59
etain@creteil.inserm.fr

Word count: article=3918 (with references); abstract=304 ; 3 tables; 38 references.

Abstract

Objective: Bipolar affective disorder (BPAD) is clinically and genetically heterogeneous and the affected phenotype is poorly defined, hampering studies of its genetic basis. Studies of specific, familial, clinical indicators of BPAD may be useful for identifying heritable forms. Homogeneous forms of the disease may be identified in patients (candidate symptom approach) and some vulnerability markers may be sought in unaffected relatives of patients (intermediate traits or endophenotypes). Physical anhedonia is considered a possible candidate symptom and endophenotype in schizophrenia, but has never been specifically investigated in BPAD.

Methods: Physical anhedonia scores (measured using Chapman's physical anhedonia scale) were compared in 351 euthymic bipolar patients, 130 of their first-degree relatives and 170 healthy controls with no personal or familial history of schizophrenia, mood disorders and suicidal behavior. We investigated intra-familial resemblance of physical anhedonia and compared the progressive and clinical characteristics of hedonic and anhedonic bipolar probands.

Results: Physical anhedonia was a stable trait in normothymic bipolar patients and significant intra-familial correlation of physical anhedonia scores was observed in bipolar families. However, physical anhedonia scores were similar in unaffected relatives and controls and the clinical characteristics of anhedonic and hedonic patients did not differ significantly. PA was not associated with an increased familial risk of bipolar disorder.

Conclusions: Physical anhedonia is a stable, familial dimension in BPAD families. It can not be considered an endophenotype, because unaffected relatives of bipolar patients and healthy controls have similar physical anhedonia scores. It also can not be considered a candidate symptom, because it does not identify a homogeneous clinical and familial subgroup of bipolar patients. Considering previous studies, physical anhedonia might be a specific candidate symptom (and endophenotype) to schizophrenia. However, the validation of this hypothesis requires replication studies in bipolar disorder and schizophrenia and further investigations in other psychiatric diseases (in particular across the mood disorder spectrum).

Key Words: Physical anhedonia, bipolar affective disorder, endophenotype, candidate symptoms, familial resemblance

INTRODUCTION

Identification of the genetic basis of bipolar affective disorder (BPAD) is hampered by the absence of a valid definition for the affected phenotype and the questionable clinical and genetic homogeneity of the disease. Indeed, the categorical diagnoses proposed by DSM-IV and ICD-10 have no proven aetiological validity (1, 2). Quantitative variables may provide a more precise and genetically valid definition of the phenotype. Such quantitative variables may be more closely related to the underlying genetic predisposition than discrete phenotypes. The "candidate symptom approach" for use in affected subjects and the "endophenotype approach" for use in unaffected relatives have been proposed as methods of clarifying the heritable phenotype in psychiatric genetics (3). The candidate symptom approach aims at identifying narrow clinical characteristics that are most likely to be associated with a disease genotype and that show a simpler pattern of inheritance (3). An endophenotype is a sub-clinical quantitative trait, also called intermediate phenotype, which correlates with the main trait of interest and can be used to define the trait or its underlying genetic mechanism more accurately (3).

Ribot first described anhedonia in 1896 as a decrease in the ability to feel pleasure (4). Chapman et al. (5) defined more precisely physical anhedonia as the inability to experience pleasure in response to physical stimuli. Physical anhedonia is suspected to be a trait-like characteristic and significantly differs from state-related anhedonia that is observed during depressive episodes (6) and that represents a core symptom of major depressive episode as defined in DSM-IV(1).

Physical anhedonia has been studied as a marker of vulnerability to schizophrenia and to endogenous depressions (7-10). However, conflicting results have been obtained, with some studies failing to distinguish schizophrenic subjects from patients with other diagnosis, particularly those with depression and other affective disorders with psychotic features. It has therefore been suggested that physical anhedonia may be a marker of predisposition to "functional psychosis" in general, rather than schizophrenia specifically (10) and that this dimension may be related to genetic loading for general psychopathology, but not for schizophrenia in particular (11, 12).

Physical anhedonia has recently been shown to be of potential value as a marker in studies of the genetic component of schizophrenia. Schürhoff *et al*. (13) identified a subgroup of schizophrenic patients with a high level of physical anhedonia. This sub-form of the disease was characterized by a greater familial risk of schizophrenia and schizophrenia spectrum

disorders and a high level of physical anhedonia among first-degree relatives. The authors also demonstrated the existence of intra-familial resemblance in the level of physical anhedonia. Therefore, physical anhedonia has been proposed as an endophenotype and a candidate symptom for schizophrenia.

In this study, we aimed at (i) investigating the familial nature of physical anhedonia in bipolar patients' families by an intra-familial correlation method, (ii) comparing the physical anhedonia scores of probands, their unaffected first-degree relatives and healthy controls and (iii) determining whether a high level of physical anhedonia in bipolar patients was associated with specific clinical characteristics and a greater familial risk of psychopathology among first-degree relatives.

MATERIALS AND METHODS

Subjects

Bipolar patients fulfilled DSM-IV (14) criteria for bipolar disorder type I or II and were interviewed by trained psychiatrists, using the French version of the Diagnostic Interview for Genetic Studies (DIGS) (15). Patients were recruited just before discharge of a hospitalisation for a (hypo)manic or major depressive episode or during their prospective follow-up in our psychiatric department. One major inclusion criteria was to be normothymic at the inclusion (i.e. having a MADRS scale score (16) and a Mania Rating Scale score (17) of no more than five).

First-degree relatives of bipolar patients were interviewed using the DIGS to assess DSM-IV axis I diagnoses. We also used the Family Interview for Genetic Studies (FIGS) (18) to investigate familial history of psychiatric disorders. Only families with at least two informative members (the proband and at least one first-degree relative) were considered for familial analyses. Best estimate procedures were applied to determine the psychiatric diagnosis of first-degree relatives.

Controls were randomly selected from blood donors at the blood transfusion centres at the Pitié-Salpétrière and Henri Mondor hospitals in Paris and Créteil. Controls were of French origin and were evaluated with the DIGS by a trained psychiatrist. To be included in the study, they had to be free of personal and first-degree familial history of mood disorders, schizophrenia spectrum disorders and suicide attempt.

Each participant was evaluated using the French version (19, 20) of the revised Physical Anhedonia Scale (PAS) developed by Chapman (5). The Physical Anhedonia Scale assesses the experience of pleasure in response to physical stimuli (taste, sight, touch and smell). It is a

61 items self-report questionnaire, with yes or no answers, each question being scored 0 or 1, the total score ranging from 0 to 61. For example, subjects were asked to answer yes or no to the following question : "the beauty of sunsets is greatly overrated". Higher scores on the physical anhedonia scale indicate greater physical anhedonia levels.

The Research Ethics Board of the Pitié-Salpétrière Hospital reviewed and approved this study. Written informed consent was obtained after complete description of the study to the subjects.

Data analysis

The significance of differences between groups was assessed using chi-squared tests for discrete variables and a two-tailed t-test for continuous variables. Non-parametric tests were used for continuous variables having distributions significantly far from normal distributions. Correlation between age and PAS score has been calculated using Spearman correlation.

Bipolar patients, their first-degree relatives and controls were not matched for socio-demographic variables (age, sex, educational level). Educational level was stratified to give three categories (I: below Bachelor's degree level, II: Bachelor's degree level, III: above Bachelor's degree level). As previous studies in different French populations (general population and students) have reported conflicting results regarding the potential effects of age, sex and educational level on PAS scores (21, 22), the effect of each variable on PAS scores were tested in each group by means of ANOVA. Considering these two arguments (unmatched groups and conflicting results in the literature), these variables were then taken into account as potential confounding factors.

We tested intra-familial correlation for physical anhedonia by means of the intra-class correlation method described by Fisher *et al*. (23) (for details, see (13)).

Bipolar probands were then classified as hedonic or anhedonic (dichotomous variable) according to the operational definition of Edell and Chapman (24). An individual was defined as anhedonic if its score was greater than the mean plus two standard deviations (calculated in the control group). An individual was defined as hedonic if its score was lower than the mean plus one half the standard deviation (calculated in the control group). We compared the course of the disease (age at onset, duration of illness), the clinical characteristics (type of bipolar disorder, suicidal behaviour, psychotic features, comorbidities with anxiety disorder and addictive disorders) and the familial history of bipolar disorder among first-degree relatives between these two groups.

The stability of PAS scores over time in a given individual was tested in a sub-sample of fifty patients, using Spearman's rank correlation coefficient.

Bonferroni's correction has been used since multiple testing was performed.

RESULTS

We included 651 subjects in this study: 351 bipolar patients (143 men, 208 women, mean age 42.6 +/-13.9 years; 260 type I bipolar patients, 91 type II bipolar patients; mean age at onset 26.5 +/-11.1 years), 130 of their first-degree relatives (54 men, 76 women, mean age 47.9 +/-17.3 years) and 170 healthy controls (98 men, 72 women, mean age 42.7 +/-9.7 years).

We included 41 mothers, 28 fathers, 21 siblings and 20 offspring in the relatives group. The relatives came from 74 families (37 families including 2 subjects, 22 families including 3 subjects and 15 including 4 or 5 subjects). Clinical evaluation of relatives with the DIGS identified lifetime mood disorders in 62 of 130 relatives (47.6%). Type I or II bipolar disorders were found in 28 relatives (21.5%) and major depressive episode (single or recurrent) in 34 relatives (26.1%). Anxiety disorders were found in 25.8% of the relatives and substance abuse/dependence in 10.1% of the relatives.

The stability of PAS scores over time in individual patients was studied in a subgroup of 50 bipolar patients. These patients were evaluated 2.6 (+/-1.9) years after their initial evaluation, with each questionnaire being completed during a normothymic period. Spearman's rank correlation coefficients showed that PAS score was stable in individuals (ρ=0.73 ; p<0.0001). This result remained significant after correction for multiple testing.

PAS scores (mean +/- SD) were given for the three groups in table 2. For bipolar patients, neuroleptic treatment at inclusion did not influence significantly PAS scores (Mann-Whitney U=8686; p=0.13). The PAS score of our control group was comparable to those obtained in various French populations, especially those recruited among general population (22, 25). It should be noted that the control group studied by Schurhoff et al. (13) was included in ours. Their respective mean PAS scores were similar : 16.8 (7.6) (n=94) versus 15.9 (+/-7.6) (n=170). Mean PAS score for bipolar patients (17.0 +/-9.0) was lower than that obtained in the schizophrenic patients (21.3 +/-9.6) that we studied in a previous study of physical anhedonia (13).

Bipolar probands, first-degree relatives and controls significantly differed in terms of age at interview (Kruskall-Wallis test H=14.1, df=2, p=0.0009), sex ratio (χ^2=14.1, df=2, p=0.0008) and educational level (χ^2=25.92 ; df=4; p<0.0001) (see table I). We found a significant effect of age on PAS scores in bipolar patients (p=0.006), in relatives (p=0.03) but not in controls (p=0.12). Age at interview and PA score were significantly correlated in bipolar probands (r=0.16, p=0.004) and relatives (r=0.24, p=0.006) but not in controls (r=0.07, p=0.33). A

significant effect of sex on PAS scores was observed for relatives (p=0.004) but not for bipolar patients (p=0.95) nor for controls (p=0.13). We found a significant effect of educational level in the three groups (bipolar patients p=0.0001, relatives p=0.01 and controls p=0.01). Age, sex and educational level were included as independent variables in multivariate analyses.

As PAS scores in bipolar patients and first-degree relatives were not normally distributed whereas those of the controls were (Shapiro-Wilk's test: $p<0.0001$; $p=0.002$; $p=0.10$ respectively), non-parametric tests were used to assess differences between groups. In comparisons of patients, relatives and controls, we used two different categories of relatives: all relatives and unaffected relatives (i.e. those with no mood disorder). PAS scores were not significantly different in bipolar patients, relatives and controls, for analyses taking into account all relatives (Kruskall-Wallis test H=0.43; df=2 ; p=0.80) and for those restricted to unaffected relatives (Kruskall-Wallis test H=0.43; df=2 ; p=0.78) (see Table II).

We carried out multivariate analysis on the subgroup of unaffected (absence of mood disorder) relatives to overcome the potential bias associated with the inclusion of affected first-degree relatives. Following the inclusion of age, sex and educational level in the multivariate model, no difference in PAS score was observed between bipolar probands, unaffected relatives and controls (ANCOVA F=0.11; df=2; p=0.89).

An intra-familial correlation for PAS scores was observed if all relatives were considered (Fisher intra-class correlation coefficient ρ=0.25, F=1.95, p=0.0004, ANOVA) or if only unaffected first-degree relatives were taken into account (ρ =0.21, F=1.63, p=0.03, ANOVA). As PAS scores of spouses were correlated (25 parental couples included) (ρ=0.38; F=2.27; p=0.02 ANOVA), we performed a last correlation analysis after having randomly excluded one parent for each pair and retaining only the unaffected relatives. The intra-familial resemblance for PAS remained significant (ρ=0.36; F=2.28; p=0.0002 ANOVA), even after correction for multiple testing.

We used Chapman's operational definition (24) to assign bipolar patients to two groups according to physical anhedonia level. Anhedonic (n=34; PAS score $\geq$ 31) and hedonic (n=249; PAS score $\leq$ 20) bipolar patients differed significantly in terms of age at interview (t-test p=0.03) but not in terms of sex ratio (χ^2 test, p=0.33). Age at onset and duration of the illness were similar for anhedonic and hedonic bipolar patients, who also did not differ in terms of type I / II bipolar disorder ratio, presence of psychotic features during episodes, personal history of suicide attempt (violent or not), alcohol and/or substance abuse, panic and anxiety disorders (see table III). Comparisons between relatives of anhedonic and hedonic

bipolar probands showed a similar frequency of bipolar disorder among relatives (21% versus 22%; χ^2 test p=0.94). The frequency of mood disorders (including bipolar disorder, unipolar disorder and major depressive episode) was similar in relatives of anhedonic bipolar probands and hedonic bipolar probands (47% versus 48% ; χ^2 test p=0.94), as was the frequency of other DSM-IV axis I diagnoses: alcohol abuse/dependence (11% versus 5% ; χ^2 test p=0.40), cannabis abuse/dependence (5% versus 7% ; χ^2 test p=0.74), anxiety disorders (21% versus 27% ; χ^2 test p=0.59).

DISCUSSION

This is the first study to investigate physical anhedonia in a large sample of bipolar patients and their first-degree relatives. The main results of this study is that physical anhedonia is a familial dimension in bipolar patients' families and that physical anhedonia scores did not differ between bipolar patients, their first degree relatives (whatever their disease status was) and healthy controls.

Physical anhedonia was found to be a stable trait in euthymic bipolar patients. This stability over time is consistent with results obtained in schizophrenic patients (26) and in control subjects (21, 27).

Physical anhedonia was clearly familial, suggesting that this psychological dimension is determined by familial factors (environmental and/or genetic). Genetic factors have been implicated in physical anhedonia in twin studies (28, 29). The intra-familial correlation observed for physical anhedonia is consistent with the results obtained in schizophrenic patients (12, 13) and in controls (11, 27). Our results suggest that physical anhedonia is a familial trait, partly under the control of genetic factors and probably inherited independently of DSM-IV axis I diagnosis, as it is observed in the general population and in bipolar or schizophrenic patients.

Physical anhedonia did not distinguish unaffected relatives of bipolar patients from controls, suggesting that this dimension is not a phenotypic marker related to predisposition to bipolar affective disorder (i.e. an endophenotype). Furthermore, the level of physical anhedonia did not identify a homogeneous clinical subgroup of bipolar patients with an increased familial risk. Clinical profile was no more severe in bipolar patients with a high level of physical anhedonia than in other patients, as previously suggested (10). The trait physical anhedonia is therefore not associated with a specific phenotypic expression of bipolar disorder and cannot be considered a candidate symptom.

Interestingly, we found that the physical anhedonia levels of spouses were significantly correlated, whereas previous studies identified no such correlation (11, 30). This resemblance between spouses may reflect assortative mating (31, 32) or may be due to marital interaction and geographic/social stratification (31). As it has been demonstrated in various populations that physical anhedonia was stable over time, this dimension is not likely to be influenced by changes in marital status. However, marital interaction can not be completely ruled out as the influence of marital status on physical anhedonia over-time stability has never be investigated. Geographic stratification is also unlikely as samples were recruited in the same geographic area. However, as educational level influenced physical anhedonia, the intra-parental correlation for physical anhedonia may be explained by spouses having similar educational levels. Indeed, 68% of parental couples were concordant for educational level.

In a previous study, we reported that physical anhedonia may be considered a candidate symptom and an endophenotype in schizophrenia (13). Considering these results and the present data, it may be suggested that this characteristic may be specific to schizophrenia. However, this interpretation reserves some comments. First, results that we obtained in schizophrenia may be interpreted as a false positive and were not replicated in other samples of schizophrenic patients. Second, to our knowledge, physical anhedonia has never been investigated in samples of remitted unipolar patients, but only in symptomatic patients (33). Thus, replication studies in independent samples of bipolar and schizophrenic patients and investigations in other mood spectrum disorders (such as unipolar disorder) may shed some light to this issue.

Some schizotypal traits might be shared between schizophrenia and bipolar disorder. Schizotypy is usually referred to a ‘liability’ to schizophrenia, but it could also be more generally referred to a non-specific ‘psychosis-proneness’ (34). Relatively little is known about the specificity of these dimension to schizophrenia. However, it should be mentioned that literature is somehow confusing as schizotypal characteristics are sometimes defined as those characteristics of schizotypal personality disorder (primarily positive symptom-focused) and sometimes defined in terms of pre-syndromal schizophrenia symptoms, including positive, negative, and disorganization symptoms. These dimensions are likely to be assessed using different questionnaires and generate various sub-dimensions. Therefore, our results are difficult to interpret in regards of previous data because of differences across assessment procedures and because schizotypy is a multidimensional concept. In spite of these methodological limitations, it should be mentioned that it has been demonstrated that bipolar patients displayed significantly more schizotypal features than controls (35). Similarly, the

Schizotypal Personality Questionnaire (36) did not discriminate between schizophrenic and bipolar patients (34). Finally, delusional proneness (37) appeared to be an inherited dimension common to both schizophrenia and bipolar disorder (38). Therefore, it should be useful to study different schizotypal measures since some of them may be specifically associated with schizophrenia while others may be shared between schizophrenia and bipolar disorder.

CONCLUSION

Physical anhedonia is a stable heritable trait displaying intra-familial correlation in bipolar families. This dimension cannot be considered an endophenotype in BPAD as it does not distinguish control subjects from individuals with a higher risk of bipolar disorder (unaffected first-degree relatives). Our results also suggest that physical anhedonia is not a candidate symptom in BPAD as different levels of physical anhedonia do not identify a subgroup of bipolar patients with specific clinical and familial characteristics. These results suggest that physical anhedonia may not constitute a shared marker of predisposition to both schizophrenia and bipolar disorder. In order to further address the specificity of physical anhedonia to schizophrenia, replication studies are required in independent samples of bipolar and schizophrenic patients and need to be extended to samples of patients with other mood spectrum disorders.

ACKNOWLEDGEMENTS

This research was supported by grants from the *Assistance Publique – Hôpitaux de Paris* (PHRC: AOM98152 and CRC94232) and the *Institut National de la Santé et de la Recherche Médicale* (Poste Accueil INSERM to F. Bellivier and B. Etain). We thank A. Mercadier, MD., JL. Beaumont, MD., B. Mignen, MD. and their collaborators (ETS Hôpital La Pitié-Salpétrière - Paris and ETS Hôpital Henri Mondor - Créteil). We thank Marie-José De Souza, Emmanuelle Abadie and Alain Philippe for providing technical assistance.

Table III : Comparison of anhedonic and hedonic bipolar probands

Sample characteristics	Bipolar probands (n=283)		p
	Hedonic	Anhedonic	
Number (%)	249 (88 %)	34 (12 %)	
Age mean (SD)	41.4 (13.9)	46.6 (13.6)	0.04 °
Sex (% of male)	41.3 %	26.5 %	0.09
Bipolar type I	73.5 %	70.6 %	0.71
Age at onset mean (SD)	26.3 (9.8)	27.1 (11.0)	0.70
Duration of illness mean (SD)	15.1 (12.1)	19.5 (11.8)	0.05 °
Familial history of bipolar disorder	42.1 %	48.4 %	0.50
Psychotic features during episodes	60.8 %	46.9 %	0.12
Suicide attempt	40.1 %	37.5 %	0.77
Violent suicide attempt	25.2 %	7.7 %	0.16
Alcohol abuse/dependence	19.8 %	15.6 %	0.57
Any substance abuse/dependence *	26.2 %	18.8 %	0.36
Panic comorbidity **	14.7 %	22.6 %	0.25
Anxiety comorbidity ***	28.8 %	41.9 %	0.13
Relatives' PAS scores mean (SD)	12.7 (4.9)	29.1 (6.4)	0.0001

* : substances including alcohol, opiates, cannabis,

** : comorbid panic disorder with or without agoraphobia

*** : comorbid panic disorder with or without agoraphobia, specific and social phobias, obsessive-compulsive disorder and generalised anxiety disorder

° : non significant after Bonferroni correction

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC; 1994.
2. World Health Organization. The ICD10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva: WHO; 1993.
3. Leboyer M. Searching for alternative phenotypes in psychiatric genetics. Methods Mol Med. 2003;77:145-61.
4. Ribot T. La psychologie des sentiments. Paris: Felix Alcan; 1896.
5. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85(4):374-82.
6. Loas G, Fremaux D, Gayant C, Boyer P. Physical anhedonia and depression: distinct concepts ? Study of the construct validity of these dimensions in a group of 224 normal subjects. Encephale. 1996;22(3):175-9.
7. Loas G, Boyer P. Anhedonia in endogenomorphic depression. Psychiatry Research. 1996;60:57-65.
8. Loas G, Boyer P, Legrand A, Gayant C, Delahousse J. Anhedonia in schizophrenia. Encephale. 1995;21(6):453-7.
9. Chapman LJ, Chapman JP. The search for symptoms predictive of schizophrenia. Schizophr Bull. 1987;13(3):497-503.
10. Katsanis J, Iacono WG, Beiser M, Lacey L. Clinical correlates of anhedonia and perceptual aberration in first- episode patients with schizophrenia and affective disorder. J Abnorm Psychol. 1992;101(1):184-91.
11. Berenbaum H, McGrew J. Familial resemblance of schizotypic traits. Psychol Med. 1993;23(2):327-33.
12. Berenbaum H, Oltmanns TF, Gottesman, II. Hedonic capacity in schizophrenics and their twins. Psychol Med. 1990;20(2):367-74.
13. Schurhoff F, Szoke A, Bellivier F, Turcas C, Villemur M, Tignol J, et al. Anhedonia in schizophrenia: a distinct familial subtype? Schizophr Res. 2003;61(1):59-66.
14. Association. AP. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC; 1994.
15. Nurnberger JJ, Blehar M, Kaufmann C, York-Cooler C, Simpson S, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry. 1994;51(11):849-59; discussion 63-4.
16. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.
17. Bech P, Rafaelsen OJ, Kramp P, Bolwig TG. The mania rating scale: scale construction and inter-observer agreement. Neuropharmacology. 1978;17(6):430-1.
18. Maxwell ME. Family Interview for Genetic Studies. Clinical Neurogenetics Branch, Intramural Research Program, NIMH. 1992.
19. Loas G. Adaptation and French validation of physical anhedonia scale: PAS (Chapman and Chapman, 1978). Encephale. 1993;19(6):639-44.
20. Loas G. French translation of the Social and Physical Anhedonia Scale of Chapman. Encephale. 1995;21(6):484.
21. Loas G, Boyer P. Evaluation of anhedonia in psychopathology: second study of the validation of the French version of the Chapman and Chapman physical anhedonia scale. Study of 356 persons. Ann Med Psychol (Paris). 1994;152(4):256-9.
22. Assouly-Besse F, Dollfus S, Petit M. French translation of the Chapman Social and Physical Anhedonia Questionnaire: validation of the French translation in controls and schizophrenic patients. Encephale. 1995;21(4):273-84.

23. Fischer R. Statistical methods for research workers. Edinburgh: Oliver and Boyd.; 1925.
24. Chapman LJ, Edell WS, Chapman JP. Physical anhedonia, perceptual aberration, and psychosis proneness. Schizophr Bull. 1980;6(4):639-53.
25. Loas G, Dubal S, Pierson A. Detection of anhedonia in the normal subject. Determination of the validity of the Chapman and Chapman (1978) revised Physical Anhedonia Scale. Encephale. 1996;22(4):301-2.
26. Herbener ES, Harrow M. The course of anhedonia during 10 years of schizophrenic illness. J Abnorm Psychol. 2002;111(2):237-48.
27. Meyer TD, Hautzinger M. Two-year stability of Psychosis Proneness Scales and their relations to personality disorder traits. J Pers Assess. 1999;73(3):472-88.
28. Hay DA, Martin NG, Foley D, Treloar SA, Kirk KM, Heath AC. Phenotypic and genetic analyses of a short measure of psychosis- proneness in a large-scale Australian twin study. Twin Res. 2001;4(1):30-40.
29. Kendler KS, Ochs AL, Gorman AM, Hewitt JK, Ross DE, Mirsky AF. The structure of schizotypy: a pilot multitrait twin study. Psychiatry Res. 1991;36(1):19-36.
30. Clementz BA, Grove WM, Katsanis J, Iacono WG. Psychometric detection of schizotypy: perceptual aberration and physical anhedonia in relatives of schizophrenics. J Abnorm Psychol. 1991;100(4):607-12.
31. Maes HH, Neale MC, Kendler KS, Hewitt JK, Silberg JL, Foley DL, et al. Assortative mating for major psychiatric diagnoses in two population-based samples. Psychol Med. 1998;28(6):1389-401.
32. Mathews CA, Reus VI. Assortative mating in the affective disorders: a systematic review and meta-analysis. Compr Psychiatry. 2001;42(4):257-62.
33. Loas G, Dhee-Perot P, Chaperot C, Fremaux D, Gayant C, Boyer P. Anhedonia, alexithymia and locus of control in unipolar major depressive disorders. Psychopathology. 1998;31(4):206-12.
34. Rossi A, Daneluzzo E. Schizotypal dimensions in normals and schizophrenic patients: a comparison with other clinical samples. Schizophr Res. 2002;54(1-2):67-75.
35. Heron J, Jones I, Williams J, Owen M, Craddock N, Jones L. Self-reported schizotypy and bipolar disorder: demonstration of a lack of specificity of the Kings Schizotypy Questionnaire. Schizophrenia Research. 2003;1898:1-6. (in press).
36. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 1991;17(4):555-64.
37. Peters ER, Joseph SA, Garety PA. Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). Schizophr Bull. 1999;25(3):553-76.
38. Schurhoff F, Szoke A, Meary A, Bellivier F, Rouillon F, Pauls D, et al. Familial aggregation of delusional proneness in schizophrenia and bipolar pedigrees. Am J Psychiatry. 2003;160(7):1313-9.