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Research report

A comparison of recovered bipolar patients, healthy relatives of bipolar probands, and normal controls using the short TEMPS-A

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Abstract

Objective: To investigate the presence of temperament dysregulation in healthy relatives of bipolar probands (RBP), a population at high risk for developing mood disorders, by comparing them with clinically recovered bipolar patients (BP) and normal controls (NC). *Method*: 52 RBP and 23 BP were originally recruited for a multicenter genetic study in bipolar disorders. NC ($n = 102$) were also recruited by newspaper advertisement, radio and television announcements, flyers, newsletters, or word of mouth. All volunteers were asked to complete the TEMPS-A Scale, a self-report questionnaire designed to measure temperamental variations in psychiatric patients and healthy volunteers. In scoring temperaments, we relied upon the short validated version of the TEMPS-A [J. Affect. Disord. (2004)], from which traits with loadings < 0.035 had been deleted. *Results*: To examine differences in temperament dimensions among the three groups, a MANCOVA model was constructed using diagnostic group as the fixed factor (BP vs. RBP vs. NC); effects of age and gender were adjusted as covariates. MANCOVA showed overall group effect on the dependent variables (Hotelling's $F_{(5,175)} = 6.64$, $p < 0.001$). Four dependent variables (dysthymic, cyclothymic, irritable, and anxious temperaments) showed significant between-group differences. RBP showed lower cyclothymic temperament scores than BP, but higher scores than NC. BP and RBP showed higher anxious temperament scores than NC. Hyperthymic scores were significantly highest in the NC. *Limitation*: In view of the small cell sizes, bipolar I vs. bipolar II subanalyses could not be conducted. *Conclusions*: Methodologic strengths of the present analyses is that the BP group had clinically recovered, and we used the validated short version of the TEMPS-A for the present analyses. Our findings suggest that some clinically healthy relatives of bipolar probands exhibit a subclinical cyclothymic instability in mood, interest, self-confidence, sleep, and/or energy as well as anxiety proneness that is not observed among normal controls. These traits may represent vulnerability markers and could presumably be used to identify individuals at high risk for developing bipolar spectrum disorders, or specific clinical subtypes (e.g., bipolar I, bipolar II) within this spectrum. This is a conceptual perspective with many unanswered questions. Resolution of these questions will require innovative definitions of phenotypes to be included in the analyses of the temperament subscales in different populations. The temperament subscales

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themselves need to be calibrated properly, to find out which traits or specific combinations of trains are most promising. More extensive and complex quantitative trait analyses of these temperaments in a much expanded sample are reported elsewhere in this issue [J. Affect. Disord. (2004)].

Keywords: Bipolar patients; Bipolar probands; TEMPS-A

1. Introduction

Official classificatory systems such as the DSM-IV and the ICD-X conceive mood disorders as a set of independent diagnostic categories sharing a core of common symptoms. This view, however, is being increasingly challenged by the description of at least seven bipolar subtypes (Akiskal and Pinto, 1999). Furthermore, family studies show that mood disorders breed together, suggesting that they may not be genetically independent (Taylor et al., 1980; Gershon et al., 1982).

A proposed solution to this question suggests that all mood disorders are part of a continuum, the bipolar spectrum (Akiskal, 1983), all differences in symptomatology reflecting but quantitative variations in genetic predisposition or in gender- and development-related factors (Akiskal, 1995; Kelsoe, 2003). This spectrum would extend from the mildest, subclinical presentations of mood disorder, the temperaments, to bipolar disorder type I and would also encompass recurrent major and minor depression, bipolar disorder type II and, potentially, other mood disorders not yet officially accepted, such as bipolar disorder types III and IV (Akiskal et al., 1977, 2003; Akiskal and Pinto, 1999). Temperaments, however, are more than just *formes frustes* of major affective disorders. Akiskal (1995), building upon the Kraepelinian position (1921), postulates that temperamental dysregulation is the fundamental pathology of mood disorders and its presence in individuals reflects an increased predisposition for developing affective disorders. Even among individuals with mood disorders, temperamental dysregulations appear to be associated with increased risk of relapse (Cassano et al., 1989) and decreased response to antidepressant medication (Koukopoulos et al., 1983).

This paper investigates the presence of temperamental dysregulation in healthy relatives of bipolar probands, a population at high risk for developing mood disorders, by comparing them with clinically recovered bipolar patients and normal controls. Given the concept of bipolar spectrum, which extends across the family (Akiskal et al., 1977), our assumption was that the degree of temperamental dysregulations measured among healthy relatives of bipolar probands would be less than that of clinically recovered bipolar patients but would exceed that of normal controls.

2. Patients and methods

Healthy relatives of bipolar probands (RBP, $n = 52$; 26 men, 26 women; age = 50.93 ± 19.29 years) and clinically recovered patients with either bipolar I ($n = 18$) or bipolar II ($n = 5$) disorders (BP, 12 men, 11 women; age = 43.03 ± 16.61 years) were recruited for a multicenter genetic study in bipolar disorders. The bipolar patients in remission were all diagnosed by the MHCRC clinical research teams using the DSM III-R for full remission (i.e. during the past 2 months, no significant signs or symptoms of the disturbance were present).

RBP volunteers did not meet current or past criteria for any Axis I and Axis II diagnosis and had at least two relatives with a mood disorder: one with bipolar disorder (I or II) and another with either bipolar disorder (I or II), schizoaffective disorder, or major depressive disorder with recurrent episodes.

The BP I, BP II and RBP groups are a subsample of a report on the genetics of quantitative traits in bipolar disorder by Evans et al. (2005), except for the fact that we have included only those who had recovered clinically. We thereby wished to exclude, to the extent possible, state effects on trait measurements.

Normal control (NC) volunteers [$n = 102$; 64 men, 38 women; age = 36.47 ± 12.33 years] were recruited by newspaper advertisement, radio and television announcements, flyers, newsletters, or word of mouth. Candidates reporting personal or family history of

mental disorders were excluded through telephone screening. All volunteers were interviewed using the Structured Clinical Interview for DSM III-R (SCID) by research fellows, psychologists, and research assistants. High inter-rater reliability has been found (Kappa scores ranged from 0.82 to 0.86).

Final diagnoses were made by consensus teams led by one of the authors (JRK). Diagnoses were derived from the combination of the SCID interview, the clinical impression of the interviewer, and a review of available medical records.

After giving written informed consent, patients were asked to complete the TEMPS-A Scale, a validated self-report questionnaire designed to measure temperamental variations in psychiatric patients and healthy volunteers (Akiskal et al., 2005a, this issue); for the present report, for scoring, we relied upon the short version of the TEMPS-A, consisting of 39 items of the original 110, selected through the Principal Components Analysis after deleting item loading of <0.035 (Akiskal et al., 2005b, this issue). Questionnaires with more than 10% of missing items were excluded from the analysis. Mean replacement was used for cases with up to three missing items.

3. Results

To examine differences in temperament dimensions among the three groups, a MANCOVA model was constructed using diagnostic group as the fixed factor (BP vs. RBP vs. NC); effects of age and gender were adjusted as covariates. Dependent variables were the five subscales of the TEMPS-A (depressive, cyclothymic, hyperthymic, irritable, and anxious temperaments). MANCOVA showed overall group effect on the dependent variables (Hotelling's $F_{(5,175)}=6.64$, $p<0.001$). Overall, age and gender showed significant covariations with group for the TEMPS-A scores ($F_{(5,168)}=4.65$, $p=0.001$ and $F_{(5,168)}=3.16$, $p<0.01$, respectively).

Four dependent variables (dysthymic, cyclothymic, irritable, and anxious temperaments) showed significant between-group differences. Estimated means are presented in Table 1. Post-hoc Bonferroni-corrected pairwise comparisons revealed significant effects on all four variables. Healthy relatives of bipolar probands showed lower cyclothymic temperament scores than recovered bipolar patients, but higher scores than normal controls ($t=-4.71$, $p<0.01$ and $t=2.66$, $p=<0.05$, respectively). Bipolar patients showed higher depressive and irritable temperament scores than healthy relatives of bipolar probands ($t=2.65$, $p<0.05$ and $t=2.94$, $p<0.01$, respectively) and normal controls ($t=2.73$, $p<0.05$ and $t=3.98$, $p<0.01$, respectively). Bipolar patients and healthy relatives of bipolar probands showed higher anxious temperament scores than normal controls ($t=3.68$, $p<0.01$ and $t=2.79$, $p<0.05$, respectively).

Table 1
MANCOVA assessing differences between recovered bipolar patients, healthy relatives of bipolar probands, and normal controls using the temperament scale scores

	Value	*F*	*p*
Hotelling	0.40	6.64	0.001

Univariate *F* test

Temperament	Recovered bipolars ($n=23$)	Healthy relatives ($n=52$)	Normal controls ($n=102$)	*F*	*p*
Depressive	1.05 ± 0.20	0.42 ± 0.14	0.45 ± 0.10	4.14	0.02
Cyclothymic	3.66 ± 0.39	1.41 ± 0.28	0.48 ± 0.19	26.283	0.001
Irritable	1.61 ± 0.23	0.78 ± 0.16	0.58 ± 0.11	7.98	0.001
Hyperthymic	3.48 ± 0.48	3.86 ± 0.34	4.50 ± 0.24	2.32	0.10
Anxious	0.80 ± 0.12	0.61 ± 0.08	0.32 ± 0.06	8.40	0.001

4. Discussion

The present analyses pertain to temperamental variations among healthy relatives of bipolar patients using the TEMPS-A. This strategy could be considered a first "litmus test" for the concept of bipolar spectrum with temperaments on its "normal" border (Akiskal, 1983, 2002). The assumptions upon which these concepts were built implied that healthy relatives of bipolar probands should exhibit a higher degree of temperamental dysregulation than normal controls. In order to enhance the contrast between these groups, we decided to include in the comparison a randomly recruited sample of clinically remitted bipolar patients.

Depressive and irritable temperament scores differentiated between recovered bipolar patients and healthy relatives of bipolar probands or normal controls. Individuals with depressive temperament exhibit low energy, low spirits, and negative cognitions.

Irritable temperament is characterized by a highly unstable mixture of dysthymic and hyperthymic traits and manifests itself in traits such as habitual complaining, overcritical attitudes, and angry outbursts (Akiskal, 1992). Our findings suggest that depressive and irritable temperaments as defined in TEMPS-A may not be pre-morbid to bipolar disorder. Rather, they might represent behavioral complications of major mood episodes.

Our main finding concerns the cyclothymic temperament, which is characterized by rapid and unpredictable mood swings between the depressive and the hyperthymic poles. Accordingly, the Temperament Scale's cyclothymic subscale was designed to assess lifelong experience of rapid shift in mood, interest, self-confidence, sleep patterns, and energy levels, rather than the symptoms of major mood episodes. We found that healthy relatives of bipolar probands exhibit cyclothymic scores that are halfway between those of bipolar patients and of normal controls. Our findings suggest that some healthy relatives of recovered bipolar probands exhibit a subclinical instability in mood, interest, self-confidence, sleep, and/or energy that is not observed among normal controls. This phenomenon may represent a vulnerability marker and could presumably be used to identify individuals at high risk for developing mood disorder. Alternatively, one might conceptualize the mood labile cyclothymia as a subthreshold expression of bipolarity (perhaps that of the bipolar II subtype, Akiskal et al., 1995; Hantouche et al., 1998).

We also found that both recovered bipolar patients and healthy relatives of bipolar probands exhibited significantly higher scores in the anxious temperament subscale than normal controls. The anxious temperament (Akiskal, 1998) is a lifelong tendency to worry about one's welfare and that of one's immediate kin, and originally hypothesized to predispose to depression, phobic disorders, and alcohol and sedative use. The present finding could be interpreted as reflecting the presence of a genetically determined predisposition (McMahon et al., 2001) to develop anxiety disorders that might account for the elevated rates of comorbidities with these disorders observed among bipolar patients (Perugi et al., 1999).

To our surprise, we found that depressive and hyperthymic temperament scores did not differentiate between healthy relatives of bipolar probands and normal controls. Actually, the hyperthymic scores were, if anything, highest (albeit nonsignificantly) in the normal controls. In a prospective study on the *offspring and siblings* of bipolar patients, Akiskal et al. (1985) reported that hyperthymic and dysthymic temperaments were present before superimposed mood episode developed. The reasons for this discrepancy remains to be elucidated. One possibility is that these two temperaments are only operative in the presence of genetic predisposition for bipolar disorder. It is also uncertain from our data whether patients with bipolar I and bipolar II disorders have different temperamental profiles, a question that could not be addressed in our investigation, given the small BP-II subsample size. In a French study, both cyclothymic and hyperthymic temperaments administered by interview showed the expected gradient, i.e. significantly lower in the relatives of normal controls (Chiaroni et al., 2005a, this issue; 2005b). Finally, to complicate matters, a Turkish study (Kesebir et al., 2005, this issue) reported that the hyperthymic was most highly represented in the clinically well relatives of classical bipolar I. The data from these different sources are difficult to reconcile. One possibility is that the SCID interview overdiagnoses bipolar I (Benazzi, 2003), which could meant that both our sample and the more expanded sample of Evans et al. (2005, this issue) could have a larger proportion of bipolar II. The relevance of cyclothymic temperament to this subtype makes greater sense on the basis of both clinical and prospective data showing high sensitivity and specificity on cyclothymic lability for bipolar II (Akiskal et al., 1995; Hantouche et al., 1998).

Nevertheless, the present study did demonstrate that several TEMPS-A Scales do differentiate among groups of bipolar patients, their healthy relatives, and normal controls, thus lending further support to the concept of a bipolar spectrum. Which specific temperaments are genetically linked to the underlying biology of the bipolar spectrum will require further studies. Finally, it is possible that such specificity is a function of discrete subtypes (e.g. bipolar I vs. bipolar II) within this spectrum. These unresolved questions represent future challenges to the methodology of quantitative trait measurement in the genetics of the bipolar spectrum (see Evans et al., 2005, this issue).

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References

Akiskal, H.S., 1983. The bipolar spectrum: new concepts in classification and diagnosis. In: Grinspoon, L. (Ed.), Psychiatry Update: The American Psychiatric Association Annual Review, vol. 2. American Psychiatric, Washington, DC, pp. 271–292.

Akiskal, H.S., 1992. Delineating irritable-choleric and hyperthymic temperaments as variants of cyclothymia. J. Pers. Disord. 6, 326–342.

Akiskal, H.S., 1995. Toward a temperament-based approach to depression: implications for neurobiologic research. Adv. Biochem. Psychopharmacol. 49, 99–112.

Akiskal, H.S., 1998. Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatr. Scand., Suppl. 393, 66–73.

Akiskal, H.S., 2002. The bipolar spectrum—the shaping of a new paradigm. Curr. Psychiatry Rep. 4, 1–3.

Akiskal, H.S., Pinto, O., 1999. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr. Clin. North Am. 22, 517–534.

Akiskal, H.S., Djenderedjian, A.H., Rosenthal, R.H., Khani, M.K., 1977. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am. J. Psychiatry 134, 1227–1233.

Akiskal, H.S., Downs, J., Jordan, P., Watson, S., Daugherty, D., Pruitt, D.B., 1985. Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. Arch. Gen. Psychiatry 42, 996–1003.

Akiskal, H.S., Maser, J.D., Zeller, P., Endicott, J., Coryell, W., Keller, M., Warshaw, M., Clayton, P., Goodwin, F.K., 1995. Switching from "unipolar" to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch. Gen. Psychiatry 52, 114–123.

Akiskal, H.S., Hantouche, E.G., Allilaire, J.F., Sechter, D., Bourgeois, M.L., Azorin, J.M., Chatenet-Duchene, L., Lancrenon, S., 2003. Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). J. Affect. Disord. 73, 65–74.

Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D., 2005a. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J. Affect. Disord. 85, 3–16 (this issue).

Akiskal, H.S., Mendlowicz, M.V., Jean-Louis, G., Rapaport, M.S., Kelsoe, M.S., Gillin, J.C., Smith, T.L., 2005b. TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament. J. Affect. Disord. 85, 45–52 (this issue).

Benazzi, F., 2003. Diagnosis of bipolar II disorder: a comparison of structured versus semistructured interviews. Prog. Neuropsychopharmacol. Biol. Psychiatry 27, 985–991.

Cassano, G.B., Akiskal, H.S., Musetti, L., Perugi, G., Soriani, A., Mignani, V., 1989. Psychopathology, temperament, and past course in primary major depressions: 2. Toward a redefinition of bipolarity with a new semistructured interview for depression. Psychopathology 22, 278–288.

Chiaroni, P., Hantouche, E.-G., Gouvernet, J., Azorin, J.-M., Akiskal, H.S., 2005a. The cyclothymic temperament in healthy controls and familially at risk individuals for mood disorder: endophenotype for genetic studies? J. Affect. Disord. 85, 135–145 (this issue).

Chiaroni, P., Hantouche, E.G., Gouvernet, J., Azorin, J.-M., Roure, L., Akiskal, H.S., 2005b. Étude psychometrique des échelles tempéramentales dépressive, hyperthymique et irritable chez 164 sujets contrôles et apparentés de patients souffrant de troubles de l'humeur. Encéphale (in press).

Evans, L., Akiskal, H.S., Keck Jr., P.E., McElroy, S.L., Sadovnick, A.D., Remick, R.A., Kelsoe, J.R., 2005. Familiality of temperament in bipolar disorder: support for a genetic spectrum. J. Affect. Disord. 85, 153–168 (this issue).

Gershon, E.S., Hamovit, J., Guroff, J.J., Dibble, E., Leckman, J.F., Sceery, W., Targum, S.D., Nurnberger Jr., J.I., Goldin, L.R., Bunney Jr., W.E., 1982. A family study of schizoaffective, I, bipolar II, unipolar, and normal control probands. Arch. Gen. Psychiatry 39, 1157–1167.

Hantouche, E.G., Akiskal, H.S., Lancrenon, S., Allilaire, J.-F., Sechter, D., Azorin, J.-M., Bourgeois, M., Fraud, J.P., Châtenet-Duchêne, L., 1998. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multisite study (EPIDEP). J. Affect. Disord. 50, 163–173.

Kelsoe, J.R., 2003. Arguments for the genetic basis of the bipolar spectrum. J. Affect. Disord. 73, 183–197.

Kesebir, S., Vahip, S., Akdeniz, F., Yüncü, Z., Alkan, M., Akiskal, H., 2005. Affective temperaments as measured by TEMPS-A in patients with bipolar I disorder and their first-degree relatives: a controlled study. J. Affect. Disord. 85, 127–133 (this issue).

Koukopoulos, A., Caliari, B., Tundo, A., Minnai, G., Floris, G., Reginaldi, D., Tondo, L., 1983. Rapid cyclers, temperament, and antidepressants. Compr. Psychiatry 24, 249–258.

Kraepelin, E., 1921. Manic-Depressive Insanity and Paranoia. E & S Livingstone, Edinburgh.

McMahon, F.J., Simpson, S.G., McInnis, M.G., Badner, J.A., MacKinnon, D.F., DePaulo, J.R., 2001. Linkage of bipolar disorder to chromosome 18q and the validity of bipolar II disorder. Arch. Gen. Psychiatry 58, 1025–1031.

Perugi, G., Akiskal, H.S., Ramacciotti, S., Nassini, S., Toni, C., Milanfranchi, A., Musetti, L., 1999. Depressive comorbidity of panic, social phobic and obsessive-compulsive disorders: is there a bipolar II connection? J. Psychiatr. Res. 33, 53–61.

Taylor, M.A., Abrams, R., Hayman, M.A., 1980. The classification of affective disorders—a reassessment of the bipolar–unipolar dichotomy. A clinical, laboratory, and family study. J. Affect. Disord. 2, 95–109.