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Research report

Familiality of temperament in bipolar disorder: support for a genetic spectrum

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Abstract

Background: The array of different diagnoses and clinical presentations seen in the family members of bipolar probands suggests a quantitative or spectrum phenotype. Consistent with this idea, it has been proposed that an underlying quantitative variation in temperament may be the primary phenotype that is genetically transmitted and that it in turn predisposes to bipolar disorder (BP). Choosing the appropriate phenotypic model for BP is crucial for success in genetic mapping studies. To test this theory, various measures of temperament were examined in the family members of bipolar probands. We predicted that a gradient of scores would be observed from those with BP to those with major depression to unaffected relatives to controls. *Methods*: Members of 85 bipolar families and 63 control subjects were administered clinical interviews for diagnosis (SCID) and two temperament assessments, the TEMPS-A and TCI-125. Subjects with BP, major depressive disorder, unaffected relatives, and controls were compared on each temperament scale and on eight factors extracted from a joint factor analysis of the TEMPS-A and TCI-125. *Results*: The four groups were found to be significantly different and with the expected order of average group scores for four of the TEMPS-A scales, three of the TCI-125 scales, and one of the extracted factors. On the fifth TEMPS-A scale, hyperthymic, controls scored higher than the other three subject groups contrary to expectations. Significant differences were seen between unaffected relatives and controls on the hyperthymic scale and on the first extracted factor, anxious/reactive. *Limitations*: Controls were mainly recruited through advertisements, which may have introduced an ascertainment bias. It is also possible that mood state at the time of completing the questionnaire influenced subject's rating of their temperament. Additionally, bipolar I and bipolar II subjects were placed in the same group even though they had some differing clinical features. *Conclusions*: Our data support the theory that some dimensions of temperament are transmitted in families as quantitative traits that are part of a broader bipolar spectrum. In particular, the hyperthymic scale of the TEMPS-A and the anxious/reactive extracted factor distinguished unaffected relatives from controls. The hyperthymic scale yielded results opposite to expectation with

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controls higher than any family group. This may be an artifact of the self-rated form of the questionnaire, a consequence of our grouping bipolar I and II subjects together, or the result of a "protective" factor and bears further study. Nevertheless, both of these scales may be useful quantitative traits for genetic mapping studies.

Keywords: TEMPS-A; TCI-125; Temperament; Bipolar spectrum; Quantitative traits; Genetics

1. Introduction

One of the greatest challenges in studying bipolar disorder (BP) genetics has been choosing the most appropriate definition of the phenotype. A wide variety of mood related traits and disorders that range from mild to severe are observed in the families of bipolar probands suggesting a complex relationship between genotype and phenotype (Gershon et al., 1982; Kelsoe, 2003; Price et al., 1985). Criteria-based categorical diagnostic systems are limited in their ability to define the variation seen in families. An alternative approach argues that BP is best conceptualized as a quantitative genetic trait with a continuous distribution rather than a discreet, qualitative one. Such a model is consistent with BP being a polygenic trait resulting from numerous interactions between genes of small effect. Within this hypothetical phenotypic distribution, the genes that predispose to BP produce a continuous variation of affective phenotypes that blend into the range of normal behavior. Under such a polygenic model, measures that allow the quantification of underlying bipolar traits would be powerful genetic tools.

The measures we explore in this paper stem from the theory that a fundamental abnormality in temperament underlies bipolarity (Akiskal, 1995, 1996; Akiskal and Akiskal, 1992; Akiskal et al., 1977). According to this theory, the fundamental trait being passed on is not the BP syndrome but variations in temperament. Thus, the more extreme the temperamental variation, the greater the risk an individual has of developing BP. Though both BP and temperament result from a biological dysregulation of mood, this model posits that temperament is the more direct and proximate effect of the biological variation. In genetic terms, this implies a higher penetrance of the trait and may ultimately prove to be a more effective and genetically powerful BP phenotype.

This theory is supported by several studies that have shown the ability of various measures of temperament to predict risk for bipolar spectrum disorders. These studies have employed several instruments for assessing temperament and demonstrated the validity of these instruments. The Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire version (TEMPS-A; Akiskal et al., 2005 (a,b)) and the Temperament and Character Inventory-125 (TCI-125; Cloninger, 1999) scales have been shown to be especially well-suited for this purpose. For example, Akiskal et al. (1977, 1979), in a prospective study of 46 subjects with a cyclothymic temperament, found that 35% developed hypomanic, manic, or depressive episodes within 3 years. In the offspring and siblings of bipolar probands (Akiskal et al., 1985), especially those with prepubertal onset of clinically relevant manifestations, as many as a third of subjects initially presented with dysthymic, cyclothymic and hyperthymic temperamental features. A study by Horwath et al. (1992) revealed that dysthymic subjects were 5.5 times more likely to develop a first-onset major depression within 1 year than those without any depressive symptoms. Kovacs et al. (1994) showed that 76% of dysthymic children ($n=55$) developed major depressive disorder (MDD) and 13% developed BP within 3–12 years. Similarly, Cassano et al. (1992) reported that 40% of 687 subjects presenting with depression had a dysthymic temperament, while 10.3% had a hyperthymic temperament. At least two studies have shown that depression is associated with low scores on the character traits of self-directedness and cooperativeness (Bayon et al., 1996; Svrakic et al., 1993), and Cloninger et al. (1994a,b) showed that depressed individuals tend to have higher scores on the temperament dimensions of harm avoidance and novelty seeking than controls, while bipolar patients tend to have TCI temperament scores that are similar to the general population.

The TCI-125 temperament scales have an additional history of positive association and linkage results in genetic studies. For instance, association

between a 48 bp repeat polymorphism in exon III of the dopamine D4 receptor (DRD4) gene and novelty seeking has been reported in two independent studies (Benjamin et al., 1996; Ebstein et al., 1996). In addition to that, significant association has also been reported between long and short variants of the serotonin transporter (5-HTT) gene-linked polymorphic region and estimated scores of harm avoidance (Lesch et al., 1996). Evidence has also been found for an interaction between the DRD4 gene and the serotonin 2C receptor gene (5-HT-2C) influencing the trait of reward dependence (Benjamin et al., 1998). Finally, significant linkage has been detected between harm avoidance and a locus on chromosome 8p21-23 in a genome-wide scan (Cloninger et al., 1998a,b), a result that was recently replicated (Zohar et al., 2003).

Temperament and character can be considered two parts of what makes up an individual's personality. Temperament has been extensively studied and defined over the years by a number of researchers, most notably by Kraepelin, Kretschmer, Cloninger, and Akiskal (von Zerssen and Akiskal, 1998). In general, temperament is defined as a person's predisposition towards certain patterns of reactivity, mood, and sensitivity, which remains stable over time and is heritable (Goldsmith et al., 1987). Character has been defined by Cloninger as a person's self-conscious goals and emotions which develop in a stepwise fashion throughout life and are shaped by a person's temperament and experiences (Cloninger, 1999). Character, in general, has been the subject of far less research than temperament and is a less well-defined idea in psychology, and some consider it not easily discriminable from the related constructs of "personality" and "temperament" (von Zerssen and Akiskal, 1998).

In this study, we examine the five scales of the TEMPS-A (Akiskal et al., 2004b), the seven scales of the TCI-125 (Cloninger, 1992), and eight extracted factors from a combined factor analysis of the TEMPS-A and TCI-125 in bipolar families and examine their utility as potential quantitative traits for use with genetic analyses. Akiskal (1996) envisions temperament as being an intermediary process on a continuum, with genetic predisposition, developmental factors, and stressors on one side and episodes of major affective disorders of the other. According to Akiskal's model, temperamental dysregulation underlies recurrent mood disorders (Akiskal, 1995; Akiskal and Akiskal, 1992). Along this line of thought, he designed the TEMPS-A as a 110 item true/false self-rated questionnaire with scales that measure dysthymic, cyclothymic, hyperthymic, irritable, and anxious temperaments (Akiskal et al., 2005a,b). An earlier version of this scale, the TEMPS-I, has been shown to have very good reliability and internal consistency, and the dysthymic, hyperthymic, and cyclothymic scales of the TEMPS-I have shown moderate stability over time (Akiskal et al., 1998; Placidi et al., 1998a,b). According to Cloninger's model, temperament and character dimensions interact to form an individual's personality with certain interactions leading to the various mood disorders as well as other psychiatric disorders. Variation on each temperament dimension is correlated with activity in specific monoaminergic systems. Variation on each character dimension has both biological and environmental underpinnings (Cloninger, 1986; Cloninger et al., 1993). In accordance with his model, Cloninger et al. (1994a,b) designed the both valid and reliable TCI-125 as a 125 item true/false self-rated questionnaire with scales that measure four temperament dimensions—harm avoidance, novelty seeking, reward dependence, and persistence—and three character dimensions—self-directedness, cooperativeness, and self-transcendence.

In designing this study, we hypothesized that control subjects and subjects with affective disorders would have significantly different scores on each temperament and character scale of the TEMPS-A and TCI-125 and on each extracted factor. In addition, we hypothesized that those related to affected individuals but unaffected themselves would have scores that were intermediate, falling between affected relatives and controls. Such a pattern would be consistent with temperament having a genetic basis rather than resulting from a mood disorder. Overall, we expected to see that BP subjects have the most pathological scores, followed by those with MDD, then the unaffected relatives, and finally the controls. Such a pattern would also be consistent with temperament being a quantitative genetic trait related to BP, and hence, suitable as an alternative phenotype for genetic analyses.

2. Materials and methods

Subjects for the study were recruited from one of three sites (San Diego, Vancouver, and Cincinnati) as part of a genetic linkage study of BP (Kelsoe et al., 2001). Families were ascertained through a proband with either bipolar I or bipolar II disorder and selected if at least two other mood disordered relatives were willing to participate. Control subjects were recruited by advertisement for participation in sleep studies and other studies at the UCSD Mental Health Clinical Research Center. Written informed consent was obtained using procedures approved by each local university IRB. Subjects were diagnosed by direct interview using the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1990) by interviewers who had undergone extensive training in its administration. DSM-III-R diagnoses were made by a panel of clinicians who reviewed the interview and information from medical records and other family informants where available.

The TEMPS-A and TCI-125 were administered to 85 BP families and 63 control subjects. Of the 383 subjects from the bipolar families taking part in this study, 109 were diagnosed as BPI, 46 as BPII, four as schizoaffective-BP type (SA-BPT), 69 as MDD-recurrent (MDD-R), 31 as MDD-single episode (MDD-SE), and 124 were not diagnosed as having a mood disorder. The family members diagnosed as BPI, BPII, or SA-BPT were placed in the BP group. Family members diagnosed as having MDD-recurrent (MDD-R) or MDD-single episode (MDD-SE) were placed into a second group, MDD. Family members were classified as unaffected relatives if they did not have any of these diagnoses, and control subjects without any psychiatric diagnosis and having no family history of any such disorders were placed into a fourth group, controls. These four groups were compared on each of the five scales of the TEMPS-A and on each of the seven scales of the TCI-125. A person's score was not used in a particular scale's analysis if they left any blanks on that scale. Also, question number 84 on the TEMPS-A was not used in the analyses because it only applies to females. Two-way ANOVA with group and sex as the two factors was employed as the primary analysis. The Tukey HSD for unequal *n*'s was utilized as a post-hoc test to compare specific groups.

All items from the TEMPS-A and TCI-125 were together subjected to varimax normalized principal factor analysis with communalities equal to multiple R^2. Factor score coefficients were utilized to compute scores for each extracted factor for all subjects. These factor scores were then compared by two-way ANOVA across the four aforementioned groups and across the sexes.

3. Results

The results using the TEMPS-A are summarized in Fig. 1. Using two-way ANOVA, significant differences were found across the four subject groups

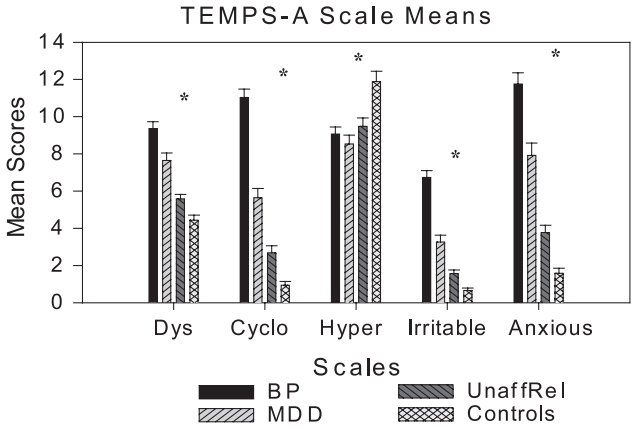

Fig.1. Mean temperament scores on the TEMPS-A by group. An * indicates that a significant difference was found across the four subject groups on that scale. Of note, the post-hoc tests revealed a significant difference between the unaffected relatives and the controls on the hyperthymic scale.

Table 1
Summary of post-hoc tests and overall hypotheses

	Dys	Cyclo	Hyper	Irritable	Anxious	Novelty	Harm	Reward	Persist	Self-D	Coop	Self-T	ANX	IMP	SPIR	WORK	GREG	EXP	SOC	CONS
BP vs. MDD[a]	++	+++	—	+++	+++	+++	—	—	—	+++	++	—	—	—	—	—	—	—	—	+
BP vs. Unaffected relatives[a]	+++	+++	—	+++	+++	+++	+++	—	—	+++	+++	+++	—	—	—	+++	—	+	—	+++
BP vs. Controls[a]	+++	+++	++	+++	+++	+++	+++	—	—	+++	+++	+++	+++	—	—	—	—	—	—	+
MDD vs. Unaffected relatives[a]	+++	+++	—	+++	+++	—	+++	—	—	+++	—	+	—	—	—	—	—	++	—	—
MDD vs. Controls[a]	+++	+++	++	+++	+++	—	+++	—	—	+++	—	+++	+++	—	—	—	—	—	—	—
Unaffected relatives vs. Controls[a]	—	—	+	—	—	—	—	—	—	—	—	—	+++	—	—	—	—	—	—	—
Affected relatives≠ Controls[b]	T	T	T	T	T	/	T	F	F	T	/	T	/	F	F	/	F	/	F	/
Unaffected relatives are between Affected relatives and Controls[b]	F	F	/	F	F	F	F	F	F	F	F	F	/	F	F	F	F	F	F	F
BP>MDD>Unaffected relatives>Controls[c]	Y	Y	N	Y	Y	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N
BP < MDD < Unaffected relatives < Controls[c]	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	Y

[a] For the post-hoc comparisons in the first section of the table, a + means that a significant difference of $P<0.05$ was found for a particular comparison, a ++ means that a $P\leq 0.01$was found, a +++ means that a $P\leq 0.001$ was found, while a — means a significant difference was not found.

[b] For the hypotheses in the second section of the table, a T means the hypothesis was found to be true for a particular scale or factor using ANOVAs and post-hoc tests, while a / meant it was only partially true by such statistical tests, and a F meant no part of the hypothesis was true.

[c] For the hypotheses in the third section of the table, a Y meant that when looking at the graphs a particular trend was found while an N meant it was not found.

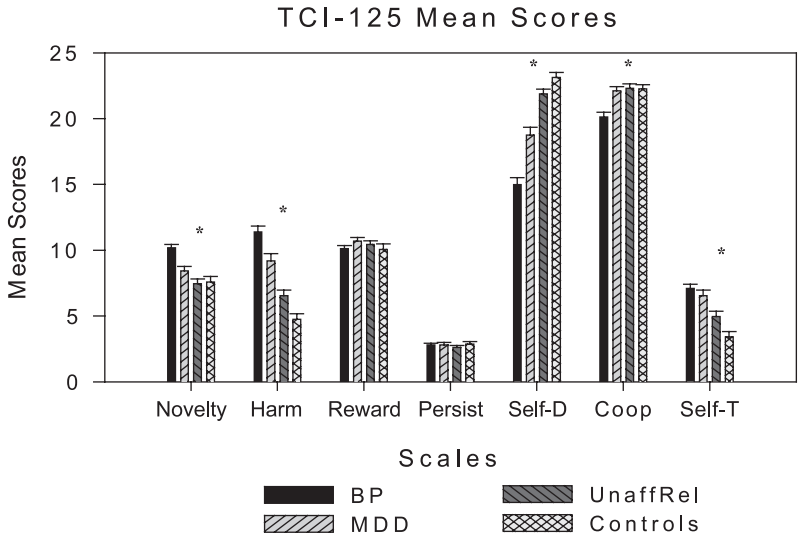

Fig. 2. Mean temperament and character scores on the TCI-125 by group. An * indicates that a significant difference was found across the four subject groups on that scale.

on all five TEMPS-A scales (dysthymic $F=32.8$, $P<0.00001$; cyclothymic $F=91.0$, $P<0.00001$; hyperthymic $F=5.8$, $P=0.0007$; irritable $F=59.6$, $P<0.00001$; and anxious $F=53.4$, $P<0.00001$). Four of the TEMPS-A scales follow the expected pattern of decreasing scores across groups. For all four of these scales, the BP group scored the highest followed by the MDD group, then unaffected relatives, and finally controls. The hyperthymic scale was quite different from the other TEMPS-A scales, with controls scoring significantly higher than the BP group, the MDD group, and unaffected relatives but with no other significant differences found. Specific post-hoc comparisons using the Tukey HSD are summarized in Table 1.

Also using two-way ANOVA, significant differences were found between the sexes on four of the five TEMPS-A scales. Females scored significantly higher than males on the dysthymic ($F=9.3$, $P=0.002$) and anxious ($F=9.8$, $P=0.002$) scales, while males scored higher on the hyperthymic ($F=5.6$, $P=0.02$) and irritable ($F=4.1$, $P=0.04$) scales. No significant difference between the sexes was seen on the cyclothymic scale ($F=0.07$, $P=0.8$). No significant interaction effects were seen between group and sex on any of the TEMPS-A scales.

As shown in Fig. 2, significant differences were found for the TCI-125 across the four subject groups on the novelty seeking ($F=15.4$, $P<0.00001$), harm avoidance ($F=32.1$, $P<0.00001$), self-directedness

Table 2
The eight factors extracted from a combined factor analysis of all the TEMPS-A and TCI-125 items

Extracted factor	Description	Eigenvalue	% Total variance	Cumulative eigenvalue	Cumulative % variance
1	Anxious/reactive	32.83193	14.03	32.83193	14.03
2	Impulsive	9.57553	4.09	42.40746	18.12
3	Spiritually connected	5.47893	2.34	47.88639	20.46
4	Motivated/hard-working	4.33582	1.85	52.22221	22.32
5	Gregarious	3.59320	1.54	55.81541	23.85
6	Hostile/explosive	3.20354	1.37	59.01894	25.22
7	Socially confident	2.69381	1.15	61.71275	26.37
8	Considerate/accepting	2.44203	1.04	64.15478	27.42

Table 3
The top 10 items by factor loading from the TEMPS-A and TCI-125 for each of the eight extracted factors from the combined factor analysis

Factor	Description	Top 10 TEMPS-A and TCI-125 items	Factor loading
Factor 1	Anxious/ reactive	(1) TEMPS-A #87: I keep on worrying about daily matters that others consider minor	(0.71760)
		(2) TEMPS-A #68: I often feel on edge	(0.67513)
		(3) TEMPS-A #86: I am always worrying about one thing or another	(0.67290)
		(4) TEMPS-A #88: I cannot help worrying	(0.66374)
		(5) TEMPS-A #92: I often feel jittery inside	(0.64656)
		(6) TCI-125 #62: It is extremely difficult for me to adjust to changes in my usual way of doing things because I get so tense, tired, or worried	(0.63389)
		(7) TEMPS-A #108: Even minor changes in routine stress me highly	(0.62773)
		(8) TEMPS-A #89: Many people have told me not to worry so much	(0.62520)
		(9) TCI-125 #46: Usually I am more worried than most people that something might go wrong in the future	(0.62332)
		(10) TEMPS-A #91: I am unable to relax	(0.62194)
Factor 2	Impulsive	(1) TCI-125 #10: I often do things based on how I feel at the moment without thinking about how they were done in the past	(0.430405)
		(2) TCI-125 #24: I often spend money until I run out of cash or get into debt from using too much credit	(0.430405)
		(3) TCI-125 #104[a]: I am usually confident that I can easily do things that most people would consider dangerous (such as driving an automobile fast on a wet or icy road)	(− 0.391951)
		(4) TEMPS-A #42: I am the kind of person who falls in and out of love easily	(0.391154)
		(5) TCI-125 #51: I am usually able to get other people to believe me, even when I know that what I am saying is exaggerated or untrue	(0.388221)
		(6) TCI-125 #103: I like to make quick decisions so I can get on with what has to be done	(0.384683)
		(7) TEMPS-A #23: I get sudden shifts in mood and energy	(0.376985)
		(8) TCI-125 #71: I often follow my instincts, hunches, or intuitions without thinking through all the details	(0.372861)
		(9) TCI-125 #106[b]: I enjoy saving money more than spending it on entertainment or thrills	(− 0.368349)
		(10) TEMPS-A #28: I often start things and then lose interest before finishing them	(0.366732)
Factor 3	Spiritually connected	(1) TCI-125 #108: I have had moments of great joy in which I suddenly had a clear, deep feeling of oneness with all that exists	(0.603381)
		(2) TCI-125 #110: I often feel like I am a part of the spiritual force on which all life depends	(0.599321)
		(3) TCI-125 #29: I sometimes feel so connected to nature that everything seems to be part of one living organism	(0.581387)
		(4) TCI-125 #73: I often feel a strong spiritual or emotional connection with all the people around me	(0.531404)
		(5) TCI-125 #42: Sometimes I have felt like I was part of something with no limits or boundaries in time and space	(0.527552)
		(6) TCI-125 #107: I have had personal experiences in which I felt in contact with a divine and wonderful spiritual power	(0.519888)
		(7) TCI-125 #43: I sometimes feel a spiritual connection to other people that I cannot explain in words	(0.507193)
		(8) TCI-125 #52: Sometimes I have felt my life was being directed by a spiritual force greater than any human being	(0.500355)
		(9) TCI-125 #114: Often when I look at an ordinary thing, something wonderful happens—I get the feeling that I am seeing it fresh for the first time	(0.431774)
		(10) TCI-125 #32: I seem to have a ‘‘sixth sense’’ that something allows me to know what is going to happen	(0.411448)

(continued on next page)

Table 3 (*continued*)

Factor	Description	Top 10 TEMPS-A and TCI-125 items	Factor loading
Factor 4	Motivated/ hard-working	(1) TCI-125 #55: I usually push myself harder than most people do because I want to do as well as I possibly can	(0.540639)
		(2) TCI-125 #22: I am usually so determined that I continue to work long after other people have given up	(0.508719)
		(3) TCI-125 #37: I am more hard-working than most people	(0.507152)
		(4) TEMPS-A #49: I am always on the go	(0.497395)
		(5) TEMPS-A #16: I am a hard-working person	(0.457083)
		(6) TEMPS-A #53: Once I decide to accomplish something, nothing can stop me	(0.449178)
		(7) TEMPS-A #58: I have abilities and expertise in many areas	(0.427958)
		(8) TCI-125 #23[c]: I often wait for someone else to provide a solution to my problems	(0.423983)
		(9) TCI-125 #122: I usually look at a difficult situation as a challenge or opportunity	(0.419006)
		(10) TCI-125 #105: I like to explore new ways to do things	(0.413555)
Factor 5	Gregarious	(1) TCI-125 #79[c]: My friends find it hard to know my feelings because I seldom tell them about my private thoughts	(0.556699)
		(2) TCI-125 #111[c]: Even when I am with friends, I prefer not to "open up" very much	(0.518679)
		(3) TCI-125 #15: I like to discuss my experiences and feelings openly with friends instead of keeping them to myself	(0.417974)
		(4) TCI-125 #96[c]: I usually like to stay cool and detached from other people	(0.416973)
		(5) TEMPS-A #10[b]: In a group, I would rather hear others talk	(−0.399749)
		(6) TCI-125 #101[c]: I wish other people did not talk as much as they do	(0.351621)
		(7) TCI-125 #30[b]: When I have to meet a group of strangers, I am more shy than most people	(−0.296628)
		(8) TCI-125 #14[c]: I am much more reserved and controlled than most people	(0.295632)
		(9) TCI-125 #64[c]: I nearly always stay relaxed and carefree, even when nearly everyone else is fearful	(0.293368)
		(10) TCI-125 #53[c]: I have a reputation as someone who is very practical and does not act on emotion	(0.284506)
Factor 6	Hostile/ explosive	(1) TCI-125 #33[a]: When someone hurts me in any way, I usually try to get even	(−0.546326)
		(2) TCI-125 #5[a]: I enjoy getting revenge on people who hurt me	(−0.516628)
		(3) TCI-125 #80[a]: I like to imagine my enemies suffering	(−0.495230)
		(4) TEMPS-A #72: When crossed, I could get into a fight	(0.462185)
		(5) TEMPS-A #71: I often get so mad that I will just trash everything	(0.427975)
		(6) TCI-125 #67[b]: I would rather be kind than to get revenge when someone hurts me	(−0.427760)
		(7) TCI-125 #88[a]: I do not think that religious or ethical principles about what is right and wrong should have much influence on business decisions	(−0.410761)
		(8) TEMPS-A #73: People tell me I blow up out of nowhere	(0.388983)
		(9) TCI-125 #13[a]: I would do almost anything legal in order to become rich and famous, even if I would lose the trust of many old friends	(−0.374539)
		(10) TCI-125 #99: I often break rules and regulations when I think I can get away with it	(0.368155)
Factor 7	Socially confident	(1) TCI-125 #86[a]: I am not shy with strangers at all	(−0.581496)
		(2) TEMPS-A #54: I am totally comfortable even with people I hardly know	(0.561380)
		(3) TCI-125 #78[a]: I feel very confident and sure of myself in almost all social situations	(−0.534029)
		(4) TCI-125 #45[a]: I would probably stay relaxed and outgoing when meeting a group of strangers, even if I were told they were unfriendly	(−0.520598)
		(5) TCI-125 #30[b]: When I meet a group of strangers, I am more shy than most people	(−0.454762)
		(6) TCI-125 #19[b]: I often avoid meeting strangers because I lack confidence with people I do not know	(−0.445303)

Table 3 (*continued*)

Factor	Description	Top 10 TEMPS-A and TCI-125 items	Factor loading
		(7) TEMPS-A #55: I love to be with a lot of people	(0.420108)
		(8) TEMPS-A #12[b]: I feel very uneasy meeting new people	(−0.365771)
		(9) TEMPS-A #43: I am usually in an upbeat or cheerful mood	(0.332963)
		(10) TEMPS-A #44: Life is a feast I enjoy to the fullest	(0.330565)
Factor 8	Considerate/ accepting	(1) TCI-125 #27[c]: I usually try to get just what I want for myself because it is not possible to satisfy everyone anyway	(0.435221)
		(2) TEMPS-A #2[b]: People tell me I am unable to see the lighter side of things	(−0.395375)
		(3) TCI-125 #18: I often consider another person's feelings as much as my own	(0.381932)
		(4) TEMPS-A #19[b]: I am the kind of person who doubts everything	(−0.377206)
		(5) TCI-125 #85[c]: I do not go out of my way to please other people	(0.345221)
		(6) TCI-125 #89: I often try to put aside my own judgments so that I can better understand what other people are experiencing	(0.329124)
		(7) TEMPS-A #81[b]: I am a very skeptical person	(−0.327611)
		(8) TEMPS-A #65[b]: I am by nature a dissatisfied person	(−0.326969)
		(9) TCI-125 #20: I like to please other people as much as I can	(0.301751)
		(10) TEMPS-A #67: I am highly critical of others	(−0.292819)

[a] These items were negatively scored by the TCI-125 and have negative factor loadings. These two things together cancel each other out when deciphering the meaning of that item. Therefore, the given statement does not need to be interpreted to say the opposite.

[b] These items have negative factor loadings and should be interpreted to mean the opposite of the given statement. For example, the ninth item under Factor 2 reads, "I enjoy saving money more than spending it on entertainment or thrills" but should be interpreted to say "I enjoy spending money on entertainment or thrills more than saving it".

[c] These items were negatively scored by the TCI-125 and should therefore be interpreted to mean the opposite of the given statement. For example, the fifth item under Factor 8 reads "I do not go out of my way to please other people" but should be interpreted to say "I do go out of my way to please other people".

($F=50.9$, $P<0.00001$), cooperativeness ($F=11.9$, $P<0.00001$), and self-transcendence ($F=13.9$, $P<0.00001$) scales using two-way ANOVA. However, no significant differences were found across the four groups on the reward dependence ($F=0.6$, $P=0.6$) and persistence ($F=0.5$, $P=0.7$) scales. Three of the TCI-125 scales showed the expected pattern of decreasing scores across groups. On the harm avoidance and self-transcendence scales, the bipolar group scored highest and the controls scored lowest, while on the self-directedness scale, the opposite was true. Specific post-hoc comparisons using the Tukey HSD are summarized in Table 1.

Significant differences between sexes were also seen on three of the TCI-125 scales. Females scored higher than males on harm avoidance ($F=6.9$, $P=0.009$), reward dependence ($F=16.5$, $P=0.00006$), and cooperativeness ($F=20.2$, $P<0.00001$). No significant difference was seen between the sexes on novelty seeking ($F=0.0002$, $P=1.0$), persistence ($F=1.5$, $P=0.2$), self-directedness ($F=1.3$, $P=0.3$), and self-transcendence ($F=0.03$, $P=0.9$). No significant interaction effects were seen between group and sex on any of the TCI-125 scales.

The joint factor analysis of the TEMPS-A and TCI-125 items initially yielded 14 factors with eigenvalues greater than 1.0, however, the later factors accounted for very small percentages of the total variance and the scree plot suggested between six and eight factors. As a result, factor analyses extracting 6–13 factors were also run. For this analysis, eight factors were chosen as this yielded the most easily interpretable results. Table 2 summarizes the eigenvalues and variances accounted for by the factors. Descriptions of these factors are as follows: Factor 1, anxious/reactive (ANX); Factor 2, impulsive (IMP); Factor 3, spiritually connected (SPIR); Factor 4, motivated/hard-working (WORK); Factor 5, gregarious (GREG); Factor 6, hostile/explosive (EXP); Factor 7, socially confident (SOC); and Factor 8, considerate/accepting (CONS). Table 3 features the items with the highest factor loadings for each extracted factor.

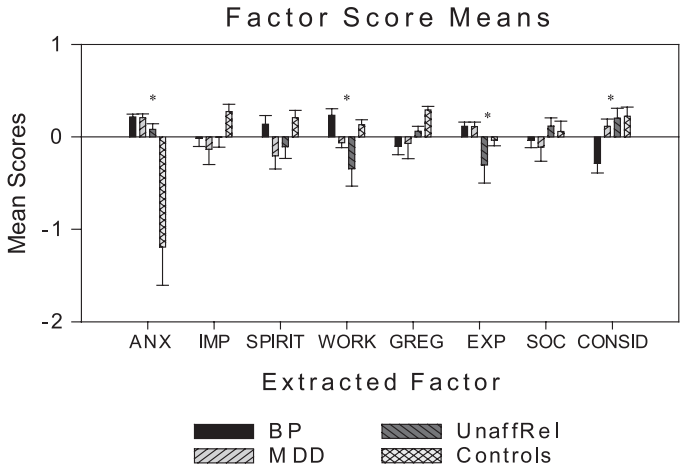

Fig. 3. Mean scores on the eight extracted factors by group. An * indicates that a significant difference was found across the four subject groups on that factor. Of note, the post-hoc tests revealed a significant difference between the unaffected relatives and the controls on the ANX factor. ANX, Factor 1 (anxious/reactive); IMP, Factor 2 (impulsive); SPIR, Factor 3 (spiritually connected); WORK, Factor 4 (motivated/hard-working); GREG, Factor 5 (gregarious); EXP, Factor 6 (hostile/explosive); SOC, Factor 7 (socially confident); CONS, Factor 8 (considerate).

As illustrated in Fig. 3, the factor scores differed significantly across the four subject groups for four of the extracted factors: ANX ($F=21.3$, $P<0.00001$), WORK ($F=6.1$, $P=0.0004$), EXP ($F=3.6$, $P=0.01$), and CONS ($F=6.9$, $P=0.0001$). IMP ($F=2.1$, $P=0.1$), SPIR ($F=1.9$, $P=0.1$), GREG ($F=2.0$, $P=0.1$), and SOC ($F=0.7$, $P=0.6$) did not show a significant group effect. Two of the extracted factors, GREG and CONS, showed the expected pattern of decreasing scores across groups. Post-hoc results are summarized in Table 1.

With regards to sex, a significant difference was found on only one of the factors, SOC. Males scored significantly higher on this factor ($F=4.3$, $P=0.04$). None of the other factors had a significant sex effect. A significant interaction effect between group and sex was found on ANX ($F=4.4$, $P=0.004$). Using post-hoc tests, control females were found to score significantly lower than all other sex group combinations ($P=0.00003$ for all comparisons except with control males where $P=0.006$). No other significant interaction effects were found.

4. Discussion

Overall, we found that the TEMPS-A scales were superior to the TCI-125 scales and extracted factors at distinguishing between our four subject groups as shown in Table 2. The unaffected relatives and control groups proved to be the most difficult to distinguish using psychometric scores, however, the hyperthymic scale of the TEMPS-A and ANX extracted factor were able to successfully make this distinction.

In reference to our hypothesis that BP subjects have the most pathological scores, followed by those with MDD, then unaffected relatives, and finally controls, we had many consistent results. On the TEMPS-A, the dysthymic, cyclothymic, irritable, and anxious scales showed this trend, while on the TCI-125, the harm avoidance, self-directedness, and self-transcendence scales followed this trend. Of the extracted factors, GREG and CONS also revealed this trend. This observation in particular is consistent with the theory that temperament is a quantitative genetic trait influencing susceptibility to BP. Results regarding all hypotheses are summarized in Table 1.

We also hypothesized that control subjects and subjects with affective disorders would have significantly different scores on the temperament and character scales of the TEMPS-A and TCI-125 and on extracted factors from the combined factor analysis. This was true for all five TEMPS-A scales, for three of the seven TCI-125 scales (harm avoidance, self-directedness, and self-transcendence), and for one of

the extracted factors (ANX). This was also partially true for two other TCI-125 scales, novelty seeking and cooperativeness, and for one of the extracted factors, CONS. For both of the TCI scales and the extracted factor CONS, the BP group was significantly different from all other groups, but the MDD group was not significantly different from controls.

A third hypothesis we had was that unaffected relatives would have scores between affected relatives and controls on the various scales. Though several scales had trends consistent with this prediction, none were statistically significant in the post-hoc comparisons. However, one scale and one extracted factor, hyperthymic and ANX, were partially consistent with this prediction. For both, controls were significantly different from the unaffected relatives. This suggests that the hyperthymic scale and ANX factor may be able to detect individuals with a genetic vulnerability even if they do not meet criteria for a DSM-IV diagnosis. This is a desirable property for defining a vulnerability phenotype for genetic linkage studies.

Our data generally support previous findings associating the various temperament traits included in the TEMPS-A with mood disorders. Previous findings implicated dysthymic, cyclothymic and hyperthymic temperaments with various affective disorders (Akiskal et al., 1977; Cassano et al., 1992; Horwath et al., 1992; Kovacs et al., 1994). Our study found that affected subjects also scored significantly higher on the dysthymic and cyclothymic scales of the TEMPS-A than unaffected subjects.

However, affected relatives did not score significantly higher on the hyperthymic scale of the TEMPS-A. In fact, the hyperthymic data looks very different from that of the other TEMPS-A scales, with controls scoring highest and no significant difference between the other three groups. Though initially designed to measure the trait of mild elevation of mood, energy, and confidence, which could lead to a mood disorder (Akiskal et al., 2005b), the hyperthymic scale measured the highest in controls. We suggest that this may be because the items for this scale have a rather positive tone for North American subjects. These items may be more frequently endorsed because they describe the kind of person society says is good and healthy. For example, one item reads, ‘‘I have great confidence in myself’’, to which the subject must respond true or false. Another item states, ‘‘I often get many great ideas’’, and a third one says, ‘‘I have abilities and expertise in many areas’’. On the TEMPS-I, the earlier, interview version of this scale, BP subjects scored higher than those without the disorder on the hyperthymic scale (Chiaroni et al., in press). These results were consistent with predictions and different from those yielded by the self-rated version we employed. This may be because an impartial interviewer was assessing the subject’s answers rather than the person assessing themselves and therefore an unintended consequence of converting the scale from interviewer rated to self-rated format. However, despite the unexpected nature of these results, the hyperthymic scale in the self-rated form was able to distinguish between unaffected relatives and controls. Perhaps this scale, in the autoquestionnaire format, is measuring idealized ‘‘normality’’ of temperament rather than hyperthymia as was originally intended. However, in a Turkish study of pure BPI probands (Kesebir et al., 2005), the hyperthymic scale of the TEMPS-A did distinguish the groups as expected. This raises the possibility that the hyperthymic scale may be more specific to that particular subform of BP, rather than groupings made on the basis of the BP spectrum (as in the present study); it is equally possible that the cultural valence of the hyperthymic scale in its self-rated version in Turkey is different from that in North America. A final consideration is the theoretical possibility that the hyperthymic scale measures a ‘‘protective’’ factor against depressive episode formation within the bipolar spectrum (Akiskal, 1995) which, in a tertiary care or university sample of BPs tends to be depression-prone (Judd et al., 2002).

A variety of findings regarding various TCI temperament traits and mood disorders have been reported. For instance, it has been shown that depressed individuals have higher scores on the harm avoidance and novelty seeking temperaments while bipolar subjects have TCI temperament scores similar to the general population (Cloninger et al., 1994a,b). In a study by Young et al. (1995), harm avoidance has been shown to be increased in both recovered unipolar and bipolar subjects while novelty seeking has been shown to be increased in bipolar subjects only when compared to normal controls. In another study, persis-

tence has been found to be significantly lower and harm avoidance and reward dependence to be significantly higher in remitted bipolars when compared to US norms (Osher et al., 1996). Two other studies found increased harm avoidance scores in depressed patients compared to normal controls and a normative Dutch sample (Hansenne et al., 1999; Marijnissen et al., 2002). Yet another study demonstrated that patients with atypical depression who did not respond to antidepressant treatment had significantly higher harm avoidance scores and significantly lower novelty seeking and persistence scores, while those who did respond to treatment had significantly higher harm avoidance and significantly lower persistence scores (Agosti and McGrath, 2002). A recent study by Farmer et al. (2003) showed that subjects with MDD scored significantly higher than control subjects on harm avoidance and scored significantly lower on novelty seeking. Both our BP and MDD subject groups, scored significantly higher than the unaffected relatives and control subject groups on the harm avoidance scale, and our BP group scored higher than unaffected relatives and controls on the novelty seeking scale. This is in complete accordance with the 1996 findings of Young et al. and also fits well with the findings of Hansenne et al. (1999); Marijnissen et al. (2002). Our TCI temperament findings only partially match those of Cloninger et al. (1994a,b); Osher et al. (1996); Agosti and McGrath (2002); Farmer et al. (2003). All of these studies including ours show a lower harm avoidance score in subjects with MDD than controls.

With regards to TCI character traits, two studies have shown that depression is associated with low scores on self-directedness and cooperativeness (Bayon et al., 1996; Svrakic et al., 1993). Another study found significantly lower scores on self-directedness and cooperativeness and significantly higher scores on self-transcendence scores in depressed patients when compared to normal controls (Hansenne et al., 1999). Similarly, cooperativeness and self-directedness were shown to be lower in MDD subjects than control subjects (Farmer et al., 2003), and atypical depression subjects who are antidepressant non-responders showed lower cooperativeness and self-directedness than controls while those who are responders only showed lower cooperativeness scores (Agosti and McGrath, 2002). One other study showed significantly lower scores on self-directedness in depressed patients compared to a normative Dutch sample (Marijnissen et al., 2002). Our results show that the BP and MDD groups scored significantly lower than unaffected relatives and controls on self-directedness and significantly higher on self-transcendence. On the cooperativeness scale, only the BP group scored significantly lower than the two unaffected groups. Our results are most similar to those of Hansenne et al. (1999), but all of these studies including ours find that subjects with MDD have lower self-directedness scores than normal controls.

A sib-pair study by Farmer et al. (2003) is the only study we were able to find that is similar to ours in that it looked at temperament and character traits in families with mood disorders. This study showed significantly increased scores in the never-depressed siblings of depressed subjects on the harm avoidance and reward dependence scales and significantly decreased scores on the novelty seeking and self-directedness scales when compared to the never-depressed siblings of the control group. We, however, did not find any significant differences between our unaffected relatives and controls on the TCI-125 scales. Perhaps this is because we were using multiplex families with a strong history of BP rather than just a proband with MDD and his or her sibling.

One potential limitation to our study that needs to be mentioned is that our controls were chiefly recruited through advertisements. Although the advertisements did not mention that this was a study of psychiatric disorders, it was mentioned in the initial screening interview. This could have biased the type of control subjects we recruited.

Another potential limitation is that, at the time of assessment, some subjects were in an affective episode while others were not. As described above, these scales have been shown to have moderate stability over time (Cloninger et al., 1994a,b; Placidi et al., 1998a), however, the longitudinal effect of state changes on temperament and character traits remains to be resolved. Studies have shown positive correlations when comparing scores on various depression scales to harm avoidance scores (Cloninger et al., 1998a,b; Farmer et al., 2003; Hirano et al., 2002; Strakowski et al., 1995) and to self-transcendence scores (Farmer et al., 2003). Negative correlations have been shown as well

when comparing scores on various depression scales and self-directedness scores (Cloninger et al., 1998a,b; Farmer et al., 2003; Hirano et al., 2002), cooperativeness scores (Cloninger et al., 1998a,b; Farmer et al., 2003; Hirano et al., 2002), and novelty seeking scores (Farmer et al., 2003). Several studies have found that successful antidepressant treatment significantly decreases harm avoidance scores (Agosti and McGrath, 2002; Chien and Dunner, 1996; Hellerstein et al., 2000; Hirano et al., 2002). The Hirano et al. (2002) study additionally found significantly increased self-directedness and cooperativeness scores after antidepressant treatment. Also found in the Hirano et al. (2002) study, however, was that harm avoidance scores were still significantly higher in antidepressant responders compared to controls even after treatment. The Agosti and McGrath (2002) study similarly found that harm avoidance scores in those who responded to antidepressants were still significantly higher than in controls even after successful treatment and the accompanying decrease in harm avoidance scores. Finally, a study by Marijnissen et al. (2002) found no change in TCI temperament and character traits after successful antidepressant treatment. These data suggest that many proposed measures of temperament actually access a mixture of trait and state. This may in part be a reporting artifact in that the subjects' view of their lifetime mood and behavior is influenced by mood state. Alternatively, trait may represent a lasting difference in baseline that predisposes to greater state variation. As we are hypothesizing that trait and state derive from the same underlying biology, this should not be surprising. It may be difficult to fully distinguish state from trait. This question requires a detailed longitudinal examination of patients across states. However, though the measures in this study may not fully distinguish trait from state, they do distinguish the different affected groups within families. This argues for the genetic validity of the measures and their possible utility in molecular genetic studies. It also should be noted that the state versus trait issue would not affect our results comparing unaffected relatives and controls.

A third potential limitation is that we grouped BPI and BPII subjects together even though there are some differences in the clinical courses of these two disorders. We were unable to find any studies which definitively showed any differences in temperament and character scale scores between BPI and BPII subjects, but people with BPI are hospitalized more often and are more likely to have psychotic symptoms than those with BPII (Vieta et al., 1997)). Also, people with BPII have a higher frequency of episodes (Coryell et al., 1989; Vieta et al., 1997), comorbid psychiatric disorders (Pini et al., 1997; Savino et al., 1993), and increased risk of suicide (Dunner et al., 1976; Goldring and Fieve, 1984; Rihmer and Kiss, 2002). Despite these differences, many have hypothesized that BPII is intermediate to BPI and MDD on a continuum of affective disorders. The affective disorders, schizoaffective disorder, BPI, BPII, and MDD, are all part of a bipolar spectrum (Akiskal, 1983; Akiskal and Pinto, 1999) with each representing a different threshold on a continuum of vulnerability created by the interactions of genetic and environmental factors (Cassano et al., 1999; Gershon et al., 1982; Nigg and Goldsmith, 1998). With this bipolar spectrum in mind, we grouped our BPI and BPII subjects together for our main analyses, however, we did run a one-way ANOVA comparing BPI and BPII subjects on each of the TEMPS-A scales and found no differences (see Table 4).

In conclusion, several measures of temperament in this sample of families provided support for the theory that temperament is a quantitative genetic trait that is related to the susceptibility to BP. These scales differed among groups and showed a relative ranking consistent with a quantitative trait. The hyperthymic scale and extracted ANX factor, in particular, distinguished controls from unaffected relatives, indicating an ability to detect genetic susceptibility. These data support the utility of employing such measures of temperament in genetic mapping studies of BP.

Table 4
A comparison of 109 BPI and 46 BPII subjects on the TEMPS-A scales

TEMPS-A scales	BPI		BPII		*F*	*P*
	Mean	S.E.	Mean	S.E.		
Dysthymic	9.21	0.43	9.78	0.68	0.503	ns
Cyclothymic	11.08	0.58	11.10	0.76	0.0003	ns
Hyperthymic	9.22	0.48	8.79	0.66	0.236	ns
Irritable	6.57	0.44	7.22	0.72	0.621	ns
Anxious	11.95	0.75	11.43	1.00	0.152	ns

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