

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Cyclothymic temperament and major depressive disorder: A study on Italian patients

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/66427> since

Published version:

DOI:10.1016/j.jad.2009.05.031

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

J Affect Disord. 2010 Mar;121(3):199-203.

doi: 10.1016/j.jad.2009.05.031.

The definitive version is available at:

<http://www.sciencedirect.com/science/article/pii/S0165032709002547>

Cyclothymic temperament and major depressive disorder: A study on Italian patients

Giuseppe Maina*, Virginio Salvi, Gianluca Rosso, Filippo Bogetto
Mood and Anxiety Disorders Unit, Department of Neuroscience, University of Turin, Italy

KEYWORDS Cyclothymic temperament. Affective temperaments, Major depressive disorder, Bipolar spectrum

* Corresponding author. Department of Neuroscience, Psychiatry Unit, University of Turin, Via Cherasco, 11, IT-10126 Turin, Italy. Tel.: +39 0116634848; fax: +39 011673473.
E-mail address: giuseppemain@hotmai.com (G. Maina).

ABSTRACT

Background: Classical authors had hypothesized that affective temperaments represent the subclinical manifestations of mood disorders: in particular, cyclothymic and hyperthymic temperaments have been considered as a subthreshold variant of bipolar disorder. The aim of our study is to test the presence of affective temperaments in a group of Italian patients with major depressive disorder (MDD), and to test the association between cyclothymic temperament and well-established validators of bipolar disorder diagnosis such as age at onset and family history of bipolar disorder.

Methods: Patients with diagnosis of major depressive disorder (DSM-IV-TR) were included in the study. Affective temperaments have been evaluated through the Italian semistructured interview version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-I). In order to improve the accuracy of family history and age at onset reports, close family members of the patients were also interviewed.

Results: 104 of patients included in the study have completed the temperament interview. 25.5% were diagnosed with a dominant affective temperament. Cyclothymic affective temperament was the most represented in the sample of MDD patients (12.3%); depressive, hyperthymic and irritable temperaments have been detected respectively in 7.5%, 2.8% and 2.8% of patients. Patients with CT showed a significantly lower age at onset of MDD than “pure” MDD patients (31.9 vs. 40.9 years; $p=0.049$) and higher rates of family history of bipolar disorder in first degree relatives (15.4% vs. 0%; $p=0.001$).

Limitations: The major limitation of this study was the lack of a group of bipolar depressives, which would have been useful in order to confirm the similarities of age at onset and bipolar family history with cyclothymic MDD.

Conclusions: Our data confirm previous reports in a sample of accurately screened patients with unipolar major depression: we found that patients with a cyclothymic temperament had an earlier age at onset and a higher family history for bipolar disorder than patients without any dominant affective temperament. Further research is needed to ascertain whether patients with “unipolar” cyclothymic MDD respond to mood stabilizers.

1. Introduction

Affective temperaments can be defined as the fundamental predisposition from which normal affective states originate, or the constitutional core of personality features that refer to reactivity, variability, and intensity of emotional dispositions (Akiskal, 1994). Some research has hypothesized that temperaments are biologically determined, correspond to peculiar neurotransmitter organizations and do not change throughout life.

Several decades ago, classical psychiatric authors have linked some of these background affective states to major affective syndromes. Kraepelin observed that cyclothymic, hyperthymic, irritable, and depressive temperaments were present before the onset of several manic-depressives, and persisted during the free intervals; these observations led him to consider affective temperaments as attenuated expressions of manias and depression as well as the background for overt clinical forms (Kraepelin, 1921). Schneider,

Table 1
Socio-demographic and clinical characteristics of N= 106 patients with Major Depressive Disorder (MDD).

	MDD	
	N/Mean	%/S.D.
Sex		
Female	84	79.2
Male	22	20.8
Age, years	51.8	16.1
Marital status		
Married	52	49.1
Divorced	5	4.7
Never married	36	34.0
Widowed	13	12.3
Educational level, years	10.7	4.1
Working level		
Unemployed	38	35.8
Blue-collar	15	14.2
White-collar	29	27.3
House-wife	20	18.9
Student	4	3.8
Age at onset of the MDD, years	38.4	15.5
Age at onset of the current MDE, years	47.8	17.5
Length of illness, years	13.5	13.3
Type of MDD		
Single episode	28	26.4
Recurrent	78	73.6
Positive family history		
At least one psychiatric disorder	44	41.5
Unipolar depressive disorders	10	9.4
Bipolar disorders	3	2.8
Loaded pedigree for mood disorders	7	8.3

although describing in detail the clinical features of depressive, cyclothymic and hyperthymic temperaments, kept them separated from manic-depressive illness (Schneider, 1958). However, affective temperaments are not placed in the current nosological systems, with some temperamental features considered as a part of personality disorders such as borderline more than subthreshold affective syndromes.

Recently, some researchers have brought back the Kraepelinian concept of affective temperaments, which have been defined as the subclinical manifestations of affective disorders. Specifically, Akiskal and colleagues have proposed that major depressive episodes (MDE) superimposed on cyclothymic temperament should be considered as a 'soft' clinical form of bipolar disorder, and treated accordingly (Akiskal and Pinto, 1999).

However, in order to include affective temperaments in the bipolar spectrum, classical validators should be used. Age at onset and family load of bipolar disorder are within the most robust clinical characteristics differentiating unipolar from bipolar disorders (Goodwin and Jamison 1990; Benazzi 2003; Perlis et al., 2006; Solomon et

al., 2006). Moreover, recent studies found that unipolar depressives displaying a young age at onset, a bipolar family history, and a high number of depressive recurrences are likely to shift to a diagnosis of bipolar disorder in the long run (Akiskal et al., 1995; Coryell et al., 1995; Geller et al., 2001; Goldberg et al., 2001; Angst et al., 2005). All these researches suggest that depression with early age at onset and a high bipolar familial load should belong to the spectrum of bipolar disorders.

The aim of our study is to test the presence of affective temperaments in a group of Italian patients with major depressive disorder (MDD), and to test the association between cyclothymic temperament and well-established validators such as age at onset and family history of Bipolar Disorder. Our hypothesis is that MDD superimposed on cyclothymic temperament is associated with earlier age at onset and more bipolar family history than MDD alone.

2. Methods

To be enrolled, patients had to fulfill the following criteria:

- a) diagnosis of major depressive disorder, single or recurrent episode, according to DSM-IV TR (SCID-I) (First et al., 1997);
- b) age between 18 and 65 years;
- c) ability to read and sign the informed consent.

The exclusion criteria for the investigation were: (a) evidence of mental retardation, lifetime history of organic mental disorders; (b) diagnosis of psychotic disorders or bipolar I and II disorders; (b) concomitant severe, unstable, active neurological or physical diseases; (c) unascertainable psychiatric history, particularly regarding past hypomanic episodes.

A 20-min interview for the assessment of temperamental characteristics was administered by a psychiatrist or psychologist with at least 2 years of postgraduate experience. This assessment was made using the Akiskal and Mallya (1987) semistructured format for hyperthymic, depressive, cyclothymic and irritable temperaments. The interview is the 32-item Italian semistructured interview version of the temperament

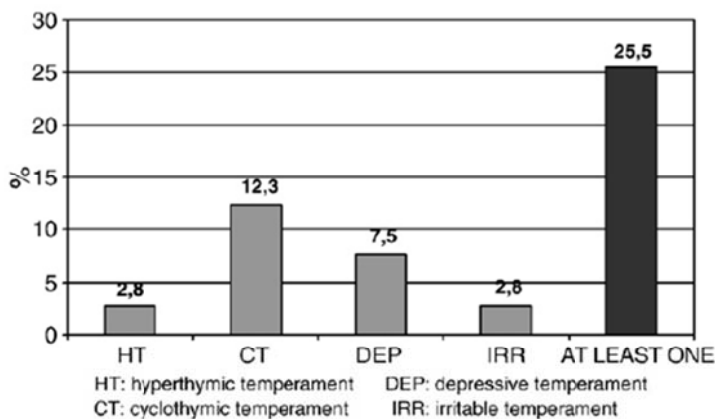


Fig. 1. Frequencies of dominant temperament in the sample of $N=106$ patients with MDE, single or recurrent.

evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-I) (Placidi et al., 1998). All interviews were conducted face-to-face with each patient included. In order to define each dominant temperament the cutoffs identified by Akiskal et al. (1998) were employed.

In the early phase of the study, inter-rater reliability on the diagnosis of Axis I disorders with the SCID-I was ascertained: Cohen Kappa Coefficient was greater than 0.80 for the presence of any current or lifetime Axis I disorder. Furthermore, inter-rater reliability for the factorial scores of hyperthymic, cyclothymic, depressive, and irritable

temperaments showed the following results: Cohen Kappa Coefficients were 0.92, 0.95, 0.91 and 0.89 respectively. In order to confirm the cyclothymic temperament (CT) as a part of the bipolar spectrum, we employed age at onset of MDD and family history for bipolar disorder as clinical “validators”, according to criteria proposed by Robins and Guze (1970). In order to improve the accuracy of family history and age at onset reports, close family members of the patients were also interviewed.

All statistical analyses were performed by SPSS software version 15.0. Between-group comparisons of categorical variables were made with the Pearson's χ^2 test, except when the expected cell size fell below 5, in which case Fisher's exact test (two-tailed) was used. Continuous variables were compared using the independent sample t-test. A p value less than 0.05 (two-tailed) was considered statistically significant.

3. Results

We included 106 patients: 28 with a single MDE, 78 with a recurrent MDE. Socio-demographic and clinical characteristics of the sample are illustrated in Table 1: the gender distribution was characterized by a higher percentage of females (79.2%); the mean age of the patients was 51.8 years.

Of the 106 patients recruited, 104 have completed the temperaments interview (TEMPS-I). The temperamental characteristics of the 104 patients are showed in Fig. 1: 25.5% of the patients were diagnosed with a dominant affective temperament. Cyclothymic affective temperament was the most represented in the sample of MDD patients (12.3%); depressive, hyperthymic and irritable temperaments have been detected respectively in 7.5%, 2.8% and 2.8% of patients. Of the 104 evaluated patients, 77 (74.5%) did not show any dominant affective temperament.

In order to validate CT as a marker of bipolar disorder, we compared the age at onset of the MDD and the presence/absence of family history for bipolar disorders in the subgroups of patients with CT versus patients without any affective temperament (“pure” MDD).

Patients with CT showed a significantly lower age at onset of MDD than “pure” MDD patients (31.9 ± 11.4 vs. 40.9 ± 15.6 ; $t=1.997$; $df=88$; $p=0.049$) and higher rates of family history of bipolar disorder in first degree relatives (15.4% vs. 0%; $\chi^2=12.115$; $df=1$; $p=0.001$) as shown in Table 2.

Finally, we compared the subgroup of CT patients with the subgroup of pure MDD patients on other clinical characteristics that have showed to be more typical of bipolar disorder (Goodwin and Jamison, 2007), in order to adjunctively confirm their bipolar nature. These analyses showed the following results: 1) CT patients showed higher rates of retarded hypersomnia (53.8% vs. 26.0%; $\chi^2=4.114$; $df=1$; $p=0.43$) and postpartum onset (30.8% vs. 3.9%; $\chi^2=11.198$; $df=1$; $p=0.001$) than “pure” MDD patients. 2) CT patients showed higher rates of cluster B personality disorders (38.5% vs. 9.1%; $\chi^2=8.303$; $df=1$; $p=0.004$) and borderline personality disorder (30.8% vs. 2.6%; $\chi^2=14.187$; $df=1$; $p=0.001$) than patients with “pure” MDD;

3) no significant differences were found in the following clinical features: psychotic or melancholic features of the MDE; high recurrence MDD (≥ 3 MDE); seasonal pattern of recurrence; Axis I Disorders comorbidity; dysphoric premenstrual disorder comorbidity.

4. Discussion

Our first objective was to assess the prevalence of affective temperaments in a sample of patients with MDD, either single or recurrent episode.

In our sample, one patient out of four displayed at least one affective temperament.

The most represented affective temperament was cyclothymic, being displayed by the 12.3% of the sample, followed by depressive, hyperthymic and irritable temperaments.

Studies on clinical samples have reported mixed results. A French study found that 33.5% of patients with a major depressive episode had a cyclothymic temperament (Akiskal et al., 2006). Another study conducted on 156 suicide attempters has reported that more than 37% of patients displayed a depressive and another 34% an irritable temperament (Rihmer et al., 2009). However, we have included only unipolars by means of accurate interviews aimed at recognizing hypomanic episodes, while the French study included all major depressives, including patients with bipolar features. Given the high prevalence of affective temperaments especially in samples of patients with bipolar disorder (Akiskal et al., 2003), our selection of strict unipolar may have downsized the prevalence rates of affective temperaments. On the other hand, patients in the Hungarian study were suicide attempters with high rate of anxiety and substance use disorders comorbidity: in such severely ill patients temperaments may be overrepresented. Finally, the TEMPS version we employed does not assess anxious temperament: since several studies performed on clinical samples have reported high prevalence of anxious temperament (Rihmer et al., 2009; Gonda et al., 2009)

this may have underestimated the rate of patients displaying at least one affective temperament.

Table 2

Validating the cyclothymic temperament as bipolar feature with age at onset and family history in patients with MDE, single or recurrent episode.

	MDD + CT (N=13)	MDD (N=77)	t/ χ^2	df	p
Age at onset of MDD, years, Mean (\pm S.D.)	31.9 (\pm 11.4)	40.9 (\pm 15.6)	1.997	88	0.049
Family history for bipolar disorders, N (%):	2 (15.4)	0 (0.0)	12.115	1	0.001

Cyclothymic temperament had been included in bipolar spectrum since 1977, when Akiskal and colleagues found that cyclothymic patients had a history of bipolar illness in biological relatives similar to bipolar I patients (30% and 26% respectively) (Akiskal et al.,1977).

More recently, assessing temperaments by using the TEMPS-I, the EPIDEP study has compared patients with bipolar disorder and MDD+cyclothymic temperament with strictly unipolar patients: the authors found an age at first seeking help comparably low and a bipolar family history comparably high for both bipolar and cyclothymic patients (Akiskal et al., 2006). Our data confirm those previous reports in a sample of accurately screened patients with unipolar major depression: we found that patients with a cyclothymic temperament had an earlier age at onset and a higher family history for bipolar disorder than patients without any dominant affective temperament.

When we controlled whether cyclothymic depressives had clinical features commonly found in bipolar patients, we found high rates of hypersomnic-retarded depression, and a postpartum onset in one-third of cyclothymic patients. Such features have been recognized as more common in bipolar than unipolar depressed patients (Goodwin and Jamison, 2007): their association with cyclothymic temperament contributes in highlighting its bipolar nature.

Of all Axis I and II psychiatric disorders, only borderline personality disorder was strongly associated with cyclothymic temperament. Since DSM-IV does not consider affective temperaments in its nosological system, cyclothymic traits such as "Mood changes without knowing why", "Enjoying people and then losing interest" or "Strong urge for risky or outrageous behavior" fall in the realm of borderline personality disorder. Some authors argue that the extreme mood lability and instability labeled as "borderline" should be instead reclassified as soft bipolarity (Akiskal et al., 2006).

In a prospective study among 559 depressed patients, bipolar converters were robustly distinguished from those with major depressive disorder who remained unipolar on the basis of high levels of mood lability, activation, and daydreaming. These clinical features resemble those found in cyclothymic temperament. The study also found that these “converters” had an early age at onset of depression (Akiskal et al., 1995). These data have recently been confirmed by a prospective study on children and adolescents those with cyclothymic–hypersensitive temperament were at high risk of presenting with a hypomanic episode over 2-years follow-up, stressing the utility to screen for temperamental characteristics even the young patients with major depression (Kochman et al., 2005).

Our study suffers from several limitations. First, there is lack of a group of bipolar depressives, which would have been useful in order to confirm the similarities of age at onset and bipolar family history with cyclothymic MDD. Second, the retrospective design may have led to inaccurate reports of age at onset; yet, age at onset of first MDE were confirmed in the present study by a family member, in an effort to validate the historical information provided by the patient; this methodology should have limited the recall bias.

Other studies have administered the TEMPS in euthymic individuals (Akiskal et al., 2005), while we interviewed currently depressed patients. It might be argued that depressed patients are biased in recalling their lifetime temperamental characteristics. However, if this were true, we would expect high rates of depressive temperaments, while more patients scored high in cyclothymic temperament scores. Furthermore, other researchers have demonstrated the liability and usefulness of administering the TEMPS in patients who were clinically depressed at interview (Mendlowicz et al., 2005; Rihmer et al., 2009). From a clinical standpoint, the applicability of the scale in unwell individuals is of great relevance for it allows identifying soft bipolar patients when there is the need to choose between treatments such as antidepressants or mood stabilizers.

In conclusion, our data give further evidence that cyclothymic temperament should be included in the bipolar spectrum. Patients with major depressive episodes superimposed on cyclothymic temperament have been defined as BP-II ½ (Akiskal and Pinto, 1999). From a clinical perspective, the compelling reason for broadening the bipolar spectrum lies in the utility of mood stabilizers as augmentation or monotherapy in the treatment of major depressive disorders with soft bipolar features. In a study 24 treatment-resistant depressed patients with cyclothymic temperament were administered lamotrigine: the 52% experienced remission that lasted at least 12 months. However, the majority of patients was bipolar II and had mixed cyclothymic/dysthymic features (Manning et al., 2005). Therefore, further research is needed to ascertain whether patients with “unipolar” MDD and cyclothymic temperament tend to respond better to mood stabilizers than antidepressants alone.

Role of funding source

None.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgement

None.

References

- Akiskal, H.S., 1994. The temperamental borders of affective disorders. *Acta Psychiatr. Scand., Suppl.* 379, 32–37.
- Akiskal, H.S., Mallya, G., 1987. Criteria for the “soft” bipolar spectrum: treatment implications. *Psychopharmacol. Bull.* 23, 68–73.
- 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., 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., Djenderedjian, A.M., 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., Placidi, G.F., Signoretta, S., Liguori, A., Gervasi, R., Maremmani, I., Mallya, G., Puzantian, V.R., 1998. TEMPS-I: delineating the most discriminant traits of cyclothymic, depressive, irritable and hyperthymic temperaments in a nonpatient population. *J. Affect. Disord.* 51, 7–19.
- Akiskal, H.S., Hantouche, E.G., Allilaire, J.F., 2003. BP-II with and without cyclothymic temperament: “dark” and “sunny” expressions of soft bipolarity. *J. Affect. Disord.* 73, 49–57.
- Akiskal, H.S., Akiskal, K., Allilaire, J.F., Azorin, J.M., Bourgeois, M.L., Sechter, D., Fraud, J.P., Chatenêt-Duchêne, L., Lancrenon, S., Perugi, G., Hantouche, E.G., 2005. Validating affective temperaments in their subaffective and socially positive attributes: psychometric, clinical and familial data from a French national study. *J. Affect. Disord.* 85, 29–36.
- Akiskal, H.S., Akiskal, K.K., Lancrenon, S., Hantouche, E., 2006. Validating the soft bipolar spectrum in the French National EPIDEP Study: the prominence of BP-II 1/2. *J. Affect. Disord.* 96, 207–213.
- Angst, J., Sellaro, R., Stassen, H.H., Gamma, A., 2005. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J. Affect. Disord.* 84, 149–157.
- Benazzi, F., 2003. Is there a link between atypical and early-onset “unipolar” depression and bipolar II disorder? *Compr. Psychiatry* 44, 102–109.
- Coryell, W., Endicott, J., Maser, J.D., Keller, M.B., Leon, A.C., Akiskal, H.S., 1995. Long-term stability of polarity distinctions in the affective disorders. *Am. J. Psychiatry* 152, 385–390.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. *Structured Clinical Interview for the Diagnostic and Statistical Manual*, Fourth Edition, Patient Version. American Psychiatric Press, Washington, DC.
- Geller, B., Zimmerman, B., Williams, M., Bolhofner, K., Craney, J.L., 2001. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. *Am. J. Psychiatry* 158, 125–127.
- Goldberg, J.F., Harrow, M., Whiteside, J.E., 2001. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am. J. Psychiatry* 158, 1265–1270.
- Gonda, X., Fountoulakis, K.N., Rihmer, Z., Lazary, J., Laszik, A., Akiskal, K.K., Akiskal, H.S., Bagdy, G., 2009. Towards a genetically validated new affective temperament scale: a delineation of the temperament phenotype of 5-HTTLPR using the TEMPS-A. *J. Affect. Disord.* 112, 19–29.
- Goodwin, F.K., Jamison, K.R., 1990. *Manic-depressive Illness*. Oxford University Press, New York, NY.
- Goodwin, F.K., Jamison, K.R., 2007. *Manic-depressive Illness*. Oxford University Press, New York, NY.
- Kochman, F.J., Hantouche, E.G., Ferrari, P., Lancrenon, S., Bayart, D., Akiskal, H.S., 2005. Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. *J. Affect. Disord.* 85, 181–189.
- Kraepelin, E., 1921. *Manic-depressive Insanity and Paranoia*. Churchill Livingstone, Edinburgh.
- Manning, J.S., Haykal, R.F., Connor, P.D., Cunningham, P.D., Jackson, W.C., Long, S., 2005. Sustained remission with lamotrigine augmentation or monotherapy in female resistant depressives with mixed cyclothymic–dysthymic temperament. *J. Affect. Disord.* 84, 259–266.
- Mendlowicz, M.V., Akiskal, H.S., Kelsoe, J.R., Rapaport, M.H., Jean-Louis, G., Gillin, J.C., 2005. Temperament in the clinical differentiation of depressed bipolar and unipolar major depressive patients. *J. Affect. Disord.* 84, 219–223.
- Perlis, R.H., Brown, E., Baker, R.W., Nierenberg, A.A., 2006. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. *Am. J. Psychiatry* 163, 225–231.
- Placidi, G.F., Signoretta, S., Liguori, A., Gervani, R., Maremmani, I., Akiskal, H.S., 1998. The semi-structured affective temperament interview (TEMPS-I): reliability and psychometric properties in 1010 14–26 year students. *J. Affect. Disord.* 47, 1–10.
- Rihmer, A., Rozsa, S., Rihmer, Z., Gonda, X., Akiskal, K.K., Akiskal, H.S., 2009. Affective temperaments, as measured by TEMPS-A, among nonviolent suicide attempters. *J. Affect. Disord.* 116, 18–22.

- Robins, E., Guze, S.B., 1970. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am. J. Psychiatry* 126, 983–987.
- Schneider, K., 1958. *Psychopathic Personalities*. Charles C. Thomas, Springfield, IL.
- Solomon, D.A., Leon, A.C., Maser, J.D., Truman, C.J., Coryell, W., Endicott, J., Teres, J.J., Keller, M.B., 2006. Distinguishing bipolar major depression from unipolar major depression with the screening assessment of depression-polarity (SAD-P). *J. Clin. Psychiatry* 67, 434–442.