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REPORT

Chronotypes of Bipolar Patients in Remission: Validation of the French Version of the Circadian Type Inventory in the FACE-BD Sample

C. Boudebesse[1,3,4], M. Lajnef[1,4], P. A. Geoffroy[1,4], F. Bellivier[4,5,6], I. Nieto[4,5], S. Gard[4,7], E. Olié[4,8], J. M. Azorin[4,9], J. P. Kahn[4,10,11], T. Bougerol[4,12], C. Passerieux[4,13], V. Aubin[4,14], V. Milhiet[1,3], S. Folkard[15,16], French Academic Centres of Expertise for Bipolar Disorders (FACE-BD) Collaborators, M. Leboyer[1,2,3,4], C. Henry[1,2,3,4], and B. Etain[1,3,4]

[1]Inserm, U955, Créteil, France, [2]Faculté de Médecine, Université Paris Est, Créteil, France, [3]Assistance Publique–Hôpitaux de Paris, Hôpital H. Mondor–A. Chenevier, Pôle de Psychiatrie, Créteil, France, [4]Fondation Fondamental, Créteil, France , [5]Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Saint-Louis–Lariboisière–Fernand Widal, Pôle Neurosciences, Paris, France, [6]Université Paris-7 Paris-Diderot, UFR de Médecine, Paris, France, [7]Hôpital Charles Perrens, Centre Expert Trouble Bipolaire, Service de Psychiatrie Adulte, Bordeaux, France, [8]Département d'Urgence et Post Urgence Psychiatrique, Centre Hospitalier Régional Universitaire Montpellier, INSERM U1061, Université Montpellier 1, Montpellier, France, [9]Départment de Psychiatrie, Hôpital Sainte Marguerite, Marseille, France, [10]Service de Psychiatrie et Psychologie Clinique, CHU de Nancy, Hôpitaux de Brabois, Vandoeuvre Les Nancy, France, [11]Université de Lorraine, Nancy, France, [12]Clinique Universitaire de Psychiatrie, CHU de Grenoble, Grenoble, France, [13]Université de Versailles Saint-Quentin, Centre Hospitalier de Versailles, Service de Psychiatrie Adulte, Le Chesnay, France, [14]Service de Psychiatrie, Centre Hospitalier Princesse-Grace, Monaco, [15]Institut de Psychologie, Université Paris Descartes, Paris, France, and [16]Body Rhythms and Shiftwork Centre, Swansea University, Swansea, Wales, UK

Circadian rhythm disturbances have been associated with bipolar disorder (BD) during both the mood episodes and the periods of remission. Circadian phase preferences for the evening have been reported for remitted patients, whereas the amplitude and stability of their rhythms have never been assessed using questionnaires. The primary aim of our study was the validation of a French version of the Circadian Type Inventory (CTI), whereas its secondary aim was the comparison between remitted patients with BD and healthy controls for rhythm stability and amplitude and for phase preference. For this purpose, we used the CTI and the Composite Scale of Morningness (CSM) that assesses phase preference (''morning'' or ''evening'' type). First, we report here on the validation of the French version of the 11-item Circadian Type Inventory in a sample of 140 remitted patients with BD and 156 healthy controls. Principal components analysis revealed a two-factor structure (FR: flexibility/rigidity scale corresponding to rhythm stability; LV: languid/vigorous scale corresponding to rhythm amplitude) explaining 52% of the variance in the control group and 47% in the bipolar group. Cronbach's alpha was 0.75 for FR and 0.73 for LV. The test-retest reliability was 0.74 for FR and 0.86 for LV (3 wks) and 0.62 for FR and 0.72 for LV (6 mos). LV and FR scores correlated with the Composite Scale of Morningness score ($p < 0.00001$ and $p = 0.0002$, respectively). Second, as compared with controls, patients with BD were more languid ($p < 0.00001$) and showed an evening preference ($p = 0.0003$), but they did not differ from the controls with regard to flexibility/rigidity. The French version of the CTI appeared to have satisfactory psychometrics characteristics. Bipolar patients exhibited not only abnormalities in phase preference but also in amplitude as measured by languidity. Since circadian rhythm dysfunction has been shown to predict poor functioning and mood relapses in interepisodic patients with BD, this tool would appear to be a promising, easy-to-use, measure of the amplitude and flexibility of circadian rhythms that could enrich the arsenal of assessments used in clinical settings.

Keywords: Amplitude, bipolar disorder, eveningness, phase, rhythms, stability

INTRODUCTION

Bipolar disorder (BD) is a severe and chronic psychiatric illness that is characterized by alternating (hypo)manic and major depressive episodes, separated by euthymic periods (American Psychiatric Association, 2000). Circadian rhythm disturbances have been associated to BD during both mood episodes and periods of remission (Etain et al., 2011; Milhiet et al., 2011).

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Correspondence: Dr. Bruno Etain, Assistance Publique–Hôpitaux de Paris, Hôpital H. Mondor–A. Chenevier, Créteil, France. E-mail: bruno.etain@inserm.fr

Compared with healthy individuals, bipolar patients in remission display blunted nocturnal melatonin rate, melatoninergic hypersensibility to light, more variable sleep-wake cycles assessed by actigraphy, sleep continuity disturbances measured with polysomnography, or abnormal fibroblast activity as assessed from the rhythmic expression patterns of clock genes. Taking account of circadian disturbances in BD has opened new avenues in pathophysiological research. Susceptibility to BD has been associated with several polymorphisms of circadian genes or melatonergic pathway genes. It is thought that circadian characteristics are potentially relevant biomarkers of BD, since they may represent the direct output of an underlying chronobiological and genetically determined susceptibility to BD (Etain et al., 2011; Leboyer & Kupfer, 2010). Moreover, consideration of the circadian disturbances in BD has led to the development and validation of new therapeutic techniques such as the interpersonal and social rhythms therapy that has been specifically conceptualized to enhance circadian rhythms' stability in bipolar patients (Frank et al., 2000) and that has been shown to reduce the likelihood of recurrence during the maintenance phase (Frank et al., 2005).

More systematic assessments of circadian (and sleep) disturbances in clinical practice may help develop novel adjunctive therapeutics and better personalize the management of BD (Henry et al., 2011; Leboyer & Kupfer, 2010). However, such assessments are not easy to use in daily practice: many involve sequential hourly measures of biochemical parameters, sleep laboratory assessment, or actigraphy, with a risk of low acceptance by patients. Access to these methods may therefore be difficult (or even impossible) for most clinicians, and these methods have thus been largely limited to research. Questionnaires represent a noninvasive method for the assessment of circadian disturbances and some have been used in BD with interesting results. Most previous studies have focused on diurnal preference and have found an association between the eveningness and BD (Ahn et al., 2008; Mansour et al., 2005; Wood et al., 2009). The advantage of such assessment is the simplicity and rapidity of use, and the correlation with many endogenous circadian phase markers, such as melatonin peak time, temperature nadir, and measures of activity/rest (Duffy et al., 2001). Although circadian rhythms may be described in terms of three main characteristics, namely the phase, amplitude, and stability of the rhythm, all previous studies in BD using self-report measures have concentrated on assessing differences in phase, and information about amplitude and stability is lacking.

The Circadian Type Inventory (CTI) is a self-assessment questionnaire first developed by Folkard et al. to improve psychometric properties of the Circadian Type Questionnaire (Folkard et al., 1979), which was designed to assess circadian phase, amplitude, and stability (Di Milia et al., 2005). The first version of the CTI consisted of 30 items and focused on circadian amplitude and stability assessment only. More specifically, the CTI describes circadian rhythms as flexible/rigid (reflecting rhythm stability) and as languid/vigorous (reflecting rhythm amplitude). For example, rigid types claim to be less able to sleep at unusual hours and languid types claim to be lethargic following reduced sleep. The two principal factors of the 30-item version explained from 23% to 27% of the variance (Silverio et al., 1997; Smith et al., 1993). Cronbach's alphas were satisfactory for the languid/vigorous scale (.74) and moderate for flexible/rigid scale (.58) (Smith et al., 1993). A revised, 18-item version was developed (Barton et al., 1995). In this revised version, the two factors explained 26% of the variance and Cronbach's alphas were 0.79 for both scales. Psychometric properties of the CTI were further improved in an 11-item version for several incremental fit indices (Di Milia et al., 2004). In this last version, the two factors explained 48% of the variance and Cronbach's alphas were high (.80) for the flexible/rigid scale and satisfactory for the languid/vigorous scale (.69). All these validation studies were performed on nonpsychiatric samples and the CTI has never previously been used on patients with BD.

The first aim of the present study was to validate a French version of the 11-item CTI, since the CTI is an easy-to use tool that could potentially be used to enrich the arsenal of assessments used in clinical settings for bipolar patients. We chose the short version because its psychometric properties are better than previous versions but until now there has not been any validated French version of the CTI available. The second aim of the study was to compare bipolar patients and healthy controls for the circadian parameters assessed by the CTI and by the Composite Scale of Morningness (CSM) (Smith et al., 1989). In combination, these two scales should capture subjective information on circadian rhythm amplitude, stability, and phase. We hypothesized that patients with BD would be more languid, more rigid, and have a greater evening preference.

METHODS

Participants and procedure

Before their inclusion, a letter of information was given to each subject and written informed consent was signed when appropriate, as required by ethical procedures in France. The experimental protocol conformed to international ethical standards (Portaluppi et al., 2010).

The bipolar patients ($n = 140$) were adult outpatients of the French Bipolar Expert Centers Network implemented within the FondaMental Foundation (FACE-BD for French Advanced Centres of Expertise in Bipolar Disorders). Inclusion criteria for patients were diagnosis of bipolar disorder, being in remission, or aged above 18 yrs. Exclusion criteria were current mood episode, current hospitalization, or aged below 18 yrs. DSM-IV

(*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) Axis I comorbidities (with past/current anxiety disorders or past alcohol/drug misuse) were not exclusion criteria. DSM-IV Axis II comorbidity was not assessed for this study. The primary diagnosis was made by psychiatrists using the Structured Interview for DSM-IV Axis I Disorders (SCID; First et al., 1995). Remission was defined by (1) a score <8 on the Young Mania Questionnaire (YMRS; Young et al., 1978); (2) a score <8 on the Montgomery and Asberg Depression Rating scale (MADRS; Montgomery & Asberg, 1979); and (3) the absence of any major mood episode according to DMS-IV criteria during the 3 mos prior to the study. Patients were recruited between February 2009 and October 2011.

The healthy controls ($n = 156$) were enrolled in an ongoing study of genetic susceptibility factors to bipolar disorder (research protocol number C08-29). Inclusion criterion for controls was aged above 18 yrs. Exclusion criteria were presence of any DSM-IV axis I psychiatric disorders or a family history of mood disorders, schizophrenia, or suicide attempts. For this purpose, controls were assessed with the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) and had no first-degree relatives with a history of mood disorders, schizophrenia, or suicide attempts (as assessed with the Family Interview for Genetic Studies) (Maxwell, 1992). Controls were recruited in Créteil (France) between June 2008 and March 2011.

All the participants completed the CTI, the CSM, the Epworth Sleepiness Scale (Johns, 1991), the MADRS, and the YMRS in a single session.

For the test-retest reliability analysis, subsamples of the bipolar patients and the healthy controls completed the CTI twice at an interval of 3 wks. To assess the temporal stability of the CTI, a subsample of the bipolar patients also completed the CTI again after 6 mos (the test-retest reliability after 3 mos in a nonclinical sample has been previously reported by Di Milia et al., 2005). In order to be included, these bipolar patients had to maintain their remission state for the 6-mo period preceding the retest.

Description of the scales

The 11-item English version of the CTI (Di Milia et al., 2005) was translated into French and then back-translated into English. The back-translation was performed by both English and French native speakers who had no prior knowledge of the scale.

The questions are concerned with daily habits and preferences. Individuals have to indicate what they prefer to do, or can do, and not what they may be forced to do due to work commitments. Each item is rated on a 5-point scale ranging from 1 (almost never) to 5 (almost always). The English version of the CTI consisted of two subscales: the flexibility/rigidity scale and the languid/vigorous scale. The flexibility/rigidity scale score is the sum of items 2, 4, 6, 8, and 10 and reflects rhythms stability. The languid/vigorous scale score is the sum of items 1, 3, 5, 7, 9, and 11 and reflects rhythms amplitude. High scores indicate a tendency towards the first of the two labels describing the dimension; that is, languid types or flexible types.

The CSM is 13-item questionnaire of diurnal preference. A lower score indicates a preference for activities in the evening. The Epworth Sleepiness Scale is an 8-item questionnaire assessing daytime sleepiness. A score above 10 indicates clinically significant daytime sleepiness. The Epworth Sleepiness Scale was used to assess the concurrent validity of the CTI. The MADRS is a 10-item questionnaire assessing current depressive symptoms. The YMRS is an 11-item questionnaire assessing current symptoms of mania. MADRS and YMRS scores below 8 correspond to the absence of depressive and manic current symptoms, respectively.

Data analysis strategy

The first aim was to examine the psychometric properties of the French version of the CTI. We studied the structure of the CTI using factor analysis with varimax rotation. Principal components analysis (PCA) requires factorizable data. To test this assumption on the CTI, the Bartlett test of sphericity (measuring the presence of correlation among matrix) and the MSA test (measure of sampling adequacy) (indicating the degree to which the variables are related) were used. A significant Bartlett test and a KMO (Kaiser-Meyer-Olkin) index above 0.60 allowed a principal components analysis to be performed. We used an orthogonal approach (varimax procedure) to determine the factorial structure of the scale. Cronbach's alpha was calculated as a measure of internal consistency. Test-retest reliability was quantified using intraclass correlation coefficients. Concurrent validity was tested using Spearman correlation tests between the CTI, CSM, and Epworth scores. The second aim of the study was to compare bipolar patients and healthy controls for circadian stability, amplitude, and phase, as assessed by the CTI and the CSM questionnaires, using nonparametric analyses (Wilcoxon test) because these variables did not fulfill the assumptions of normality. Skewness and kurtosis values in the whole sample were calculated. Data analysis was conducted using the R program (R version 2.13.0) (R core team, 2013).

RESULTS

Participants

Sociodemographic and clinical characteristics of the sample are described in Table 1. Samples were similar for age and sex ratio. Although the differences were not clinically significant, bipolar patients exhibited higher scores than controls on the MADRS and the YMRS.

TABLE 1. Sociodemographic and clinical characteristics of the sample.

Characteristics	Bipolar group ($n=140$)	Control group ($n=156$)	Statistics for Wilcoxon, Chi^2 and t test
Age, mean (SD)	41.57 (12.6)	42.04 (11.5)	$Z=0.87$ $p=0.38$
Sex, F/M (%F)	72/68 (51%)	84/72 (53%)	$\chi^2=0.17$, $df=1$, $p=0.67$
MADRS, mean (SD)	2.97 ± 2.34	0.62 ± 1.21	$t=-10.35$, $df=294$, $p<0.0001$
YMRS, mean (SD)	1.32 ± 1.87	0.15 ± 0.46	$t=-7.17$, $df=294$, $p<0.0001$
BD subtype I (% of patients)			
Type I	60.7%		
Type II	32.2%		
Type NOS	7.1%		
Age at onset of BD, mean (SD)	25.44 ($\pm$10)		
Duration of illness, mean (SD)	16.1 ($\pm$10.3)		
Number of major mood episodes,mean (SD)	6.2 ($\pm$4.4)		
Lifetime history of suicide attempt(% of patients)	33.3%		
Lifetime history of rapid cycling(% of patients)	14.5%		

SD = standard deviation; df = degree of freedom; NOS: not otherwise specified.

TABLE 2. PCA of the CTI in the control group.

Control group	Eigen value	Percentage of variance	Cumulative percentage of variance
Factor 1	3.11	28.28	28.28
Factor 2	2.59	23.57	51.85
Factor 3	1.12	10.16	62.01

TABLE 3. PCA of the CTI in the bipolar group.

Bipolar group	Eigen value	Percentage of variance	Cumulative percentage of variance
Factor 1	2.88	26.06	26.06
Factor 2	2.25	20.48	46.54
Factor 3	1.05	9.55	56.09

TABLE 4. Factor loadings.

Factor	Bipolar group	Control group
Factor 1 = flexible/rigid scale		
Item 2	0.75	0.74
Item 4	0.62	0.80
Item 6	0.44	0.47
Item 8	0.39	0.39
Item 10	0.75	0.79
Factor 2 = languid/vivid scale		
Item 1	0.58	0.77
Item 3	0.24	0.32
Item 5	0.63	0.54
Item 7	0.57	0.77
Item 9	0.54	0.66
Item 11	0.62	0.38

Principal components analysis

In both bipolar and control groups, Bartlett tests of sphericity (measuring the presence of correlation among matrix) were significant (<0.0001) and the Kaiser-Meyer-Olkin measure of sampling adequacy (>0.70) showed that these samples were appropriate for the factor analysis. The results of the PCA in the bipolar group and in the control group are reported in Tables 2 and 3, respectively. According to the Keiser-Guttman rule that retains factors with Eigen values above unity, the PCA resulted in three principal factors in both groups. These three factors accounted for 62.01% of the variance in the control group and for 56.09% of the variance in the bipolar group. However, factor 3 consisted of a single item (item 3) in both groups and in line with Horn parallel analysis, only two principal factors were retained. Item 3 was incorporated into factor 2, as its loading on this factor in the whole sample was close to 0.4. This two-factor model explained 52% of the variance in the controls and 47% in the BD cases.

Factor loadings

Loadings on the two principal factors of the CTI in the two groups are presented in Table 4. A similar item composition of factors 1 and 2 was observed in both groups. Factor 1 consisted of items 2, 4, 6, 8, and 10 and hence was identical to the flexibility/rigidity scale (FR) of the English version. Factor 2 consisted of items 1, 3, 5, 7, 9, and 11 and was the same as the languid/vigorous scale (LV) of the English version. The correlations between the components were small, suggesting they are assessing different constructs (rho = −0.06, $p=0.49$ for patients and rho = −0.10, $p=0.23$ for controls). FR explained 28.3% and 26.1% of the variance, and LV explained 23.6% and 20.5% of the variance, respectively, in the controls and bipolar patients.

Internal reliability

The CTI was examined for internal consistency in the whole sample ($N=293$). Cronbach's alpha was 0.75 for FR and 0.73 for LV.

Test-retest reliability

For the test-retest analysis, the CTI was completed two times at a 3-wk interval by remitted bipolar patients (n = 28) and healthy controls (n = 28). Considering the whole subgroup (n = 56), the test-retest correlation coefficient was 0.74 for FR and 0.86 for LV. Some bipolar patients (n = 19) completed the CTI two times at a 6-mo

TABLE 5. Comparison between the bipolar and the control groups for CTI and CSM scores.

Score	Bipolar Group (n = 140) Mean (SD)	Control group (n = 156) Mean (SD)	Statistics Wilcoxon
Languid/vivid score	18.71 (4.6)	16.31 (4.5)	$p < 0.00001$
Flexible/rigid score	13.58 (4.1)	14.16 (4.2)	$p = 0.19$
CSM	36.27 (8.3)	39.64 (7.9)	$p = 0.0003$

interval and here the test-retest correlation coefficient was 0.62 for the FR and 0.72 for LV.

Concurrent validity

Spearman correlation coefficients were used to assess the concurrent validity of the CTI with the CSM and the Epworth Sleepiness Scale in the whole sample (bipolar patients + healthy controls). LV scores correlated significantly with the CSM scores (rho = −0.62, $p < 0.00001$) and with the Epworth Sleepiness Scale scores (rho = 0.21, $p = 0.0003$). The FR scores correlated significantly with the CSM scores (rho = −0.21, $p = 0.0002$) but not with the Epworth Sleepiness Scale scores (rho = 0.009, $p = 0.87$).

Comparison of CTI and CSM Between Remitted Bipolar Patients and healthy controls

The results of the comparisons between bipolar patients and healthy controls for CTI FR, CTI LV, and CSM scores are summarized in Table 5. In the whole sample, for the two CTI scores, skewness and kurtosis are as followed (CTI FR skewness = 0.19; kurtosis = −0.37 ; CTI LV skewness = −0.04 ; kurtosis = −0.46). Since the CTI scores did not differ between bipolar type I and type II patients (data not shown), no stratification of subtypes was made. Patients with bipolar disorder were significantly more languid than healthy controls ($p < 0.00001$), but there was no significant difference with respect to the flexibility/rigidity scale. Patients with bipolar disorder also showed a significantly greater evening preference compared with healthy controls ($p = 0.0003$). It should be noted that a sample size of at least 140 cases and 140 controls provides a power of 99% for CTI LV, of 24% for CTI FR, and of 92% for CSM.

DISCUSSION

The first aim was to validate the French version of the CTI in a nonclinical sample and in patients with BD. The PCA showed a two-factor solution that was the same as the original division of the CTI into two subscales of flexibility/rigidity and languid/vigorous. The internal consistency was satisfactory for both factors and similar to the Cronbach's alpha coefficients reported for the English version (Di Milia et al., 2005). Results obtained regarding explained variance, concurrent validity, and test-retest reliability indicated that this French version of the CTI has satisfactory psychometrics properties and can be recommended for use in both nonclinical and clinical samples, such as patients with BD (and possibly extended to other mood disorders).

The second aim of the study was to characterize the circadian trait features of bipolar patients compared with healthy controls. The CTI was chosen to measure circadian stability and amplitude, and the CSM to assess circadian phase preference. First, we replicated the association between BD and evening preferences that has been suggested by several previous studies using the ''classical'' CSM (Ahn et al., 2008; Mansour et al., 2005; Wood et al., 2009) or interviews (Giglio et al., 2010a). Secondly, we found that bipolar patients not only differed in their phase preferences but were also significantly more languid than healthy participants, i.e., they reported a higher sensitivity to sleep reduction and were more lethargic following reduced sleep. This implies a lower amplitude of their circadian rhythms, and this is consistent with lower amplitude of the melatonin peak at night (Nurnberger et al., 2000) and of the activity rhythm measured by actigraphy (Indic et al., 2011; Jones et al., 2005). We found no difference in flexibility/rigidity despite our expectation of more rigid rhythms in bipolar patients, i.e., a greater sensitivity to unusual schedules in bipolar patients. Indeed, BD patients show reliably greater variability of actigraphic parameters (Ritter et al., 2012) and lower daily lifestyle regularity as assessed by the Social Rhythm Metrics (Bullock et al., 2011; St-Amand et al., 2013). In sum, our data suggest that BD patients differ from controls not only in terms of their phase preference, but also in terms of the amplitude, but not the stability, of their circadian rhythms.

Languid typology has been associated with more lethargic feelings following reduced sleep, more difficulties with overcoming drowsiness, and a greater need for sleep (Di Milia et al., 2005). There could be a link between circadian disturbances and the sleep disturbances observed in bipolar patients (Harvey, 2008). Evening types have been associated with various dimensions of personality (Hsu et al., 2012), including some emotional and affective temperaments (Ottoni et al., 2011), proneness to depression (Hidalgo et al., 2009), impulsivity (Selvi et al., 2011), and memory and attentional problems (Schmidt et al., 2007). It is noteworthy that all of these dimensions are overrepresented amongst bipolar patients. These circadian phenotypes might also be related to the health problems of bipolar patients, and in particular comorbid somatic conditions such as increased body fat (Soreca et al., 2009). Further, they may be related to the patients' difficulties in adjusting to the disruption of their social routines occasioned by the onset of new mood episodes. This follows from the social zeitgeber (time giver) theory, which suggests that patients with BD may have susceptible internal circadian oscillators, resulting in less adaptability and hence contributing to the occurrence of affective dysregulation (Ehlers et al., 1988; Grandin et al., 2006). Harvey proposed a model for BD that

integrates genetic susceptibility, sleep and circadian functioning, neurotransmitter output, and mood deregulation (Harvey, 2008). According to this model, some genetic variants of candidate genes (mainly circadian ones) predispose individuals to being relatively less able to adapt their circadian rhythms appropriately to their environment, and to being prone to sleep disturbances. Since circadian and neurotransmission systems are highly connected, circadian and/or sleep-related abnormalities may affect the functioning of the dopamine and serotonin circuitry, which in turn may affect mood regulation.

Further studies should help to clarify how the CTI (possibly used in conjunction with the CSM) may contribute to a better understanding of the chronobiological determinants of BD. Studies among nonaffected relatives of bipolar patients, leading to heritability estimates of CTI components, and of the correlation between circadian genes polymorphisms and circadian phenotypes would be of great interest (Etain et al., 2011). Prospective studies might also consider testing whether the circadian characteristics assessed by the CTI are likely to predict the response to treatments influencing circadian rhythms (known as ''chronotherapeutics''). Lithium, the gold standard of mood stabilizers, produces a lengthening of the circadian period, enhances the amplitude of the PER2 protein rhythms in the central and peripheral circadian clock (Abe et al., 2000), and acts on the melatonergic system, since low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers (Hallam et al., 2005b). This latter property is shared with valproate sodium, another mood stabilizer (Hallam et al, 2005a). The CTI may help to distinguish between good and bad responders to these treatments and thus help to define personalized treatment.

The main limitation of this study was the potential confounding of BD with treatment, since the all-bipolar patients were receiving (combinations of) psychotropic medications that may have influenced the differences observed between the groups. Such a confounding effect has previously been reported (Wood et al., 2009), although it is controversial (Mansour et al., 2005). Further investigation of the potential effect of psychotropic drugs on circadian parameters is therefore highly recommended. Further, the analyses failed to control for the current level of employment, which may also act as a confounding factor. Nor can we definitively exclude any effect of current mood symptoms, although the patients were all assessed during a period of remission. The polarity of the last major episode also represents a potential confounding factor that we were unable to control. In addition, our sample size may have been insufficient to detect a potential difference between patients and controls on the CTI flexibility/rigidity scale. Likewise we had only a small sample size for the test-retest reliability analyses. Finally, we were unable to test the concurrent validity of the CTI against more objective measures such as the circadian melatonin secretion profile or actigraphy. We are currently conducting a study to examine the relationship between the CTI factors and actigraphy measures of circadian amplitude and stability.

In conclusion, the French version of the CTI has been validated in a sample of bipolar patients assessed in a French network of bipolar expert centers and in healthy participants. The CTI offers a noninvasive (but indirect) assessment of circadian rhythms among bipolar patients and may be useful in daily clinical practice to measure circadian parameters in this population. Since circadian rhythm dysfunction has been shown to predict functioning in interepisodic patients with BD (Giglio et al., 2010b) and to be a risk factor for relapses, the CTI would appear to be a promising, easy-to use, measure of the amplitude and flexibility of circadian rhythms that could enrich the arsenal of assessments used in clinical settings (Henry et al., 2011).

LIST OF FACE-BD COLLABORATORS

FACE-BD Clinical Coordinating Center (FondaMental Foundation)
C. Henry, M. Leboyer, B. Etain

FACE-BD Data Coordinating Center (FondaMental Foundation)
H. Laouamri, N. Ngo-Nguyen

FACE-BD Clinical Sites and Principal Collaborators in France

AP-HP, Hôpital H. Mondor–A. Chenevier, Pôle de Psychiatrie, Créteil
C. Boudebesse, A. Raust, A. Leduc, C. Daban, S. Lauer

AP-HP, GH Saint-Louis–Lariboisière–Fernand Widal, Pôle Neurosciences, Paris
F. Bellivier, J. P. Lépine, I Nieto, M. Leroux, S. Sportiche, C. Bernardon, I. Biseul, P. Seguin

Hôpital C. Perrens, Centre Expert Trouble Bipolaire, Service de Psychiatrie Adulte, Pôle 3-4-7, Bordeaux
B. Antoniol, S. Gard, A. Desage, K Mbailara, A. Jutant, I. Minois, L. Zanouy

Département d'Urgence et Post Urgence Psychiatrique, CHRU Montpellier, Montpellier
P. Courtet, E. Olié, F. Molière, L. Chaib, G. Tarquini, Z. Kaouachi, M. Seyller, C. Kindelberger

Départment de Psychiatrie, Hôpital Sainte Marguerite, Marseille
J. M. Azorin, R. Belzeaux, N. Corréard

Service de Psychiatrie et Psychologie Clinique, CHU de Nancy, Hôpitaux de Brabois, Vandoeuvre Les Nancy
J. P. Kahn, P. Kieffer, O. Wajsbrot-Elgrabli, R. Cohen

Clinique Universitaire de Psychiatrie, CHU de Grenoble, Grenoble
T. Bougerol, M. Polosan, M. A. De Pourtales, S. Garçon, B. Fredembach

Centre Hospitalier de Versailles, Service de Psychiatrie Adulte, Le Chesnay
M. C. Hardy-Bayle, C. Passerieux, N. Kayser, I. Grévin, M. Urbach, G. Linares, L. Polaillon

Service de Psychiatrie, Centre Hospitalier Princesse-Grace, Monaco
V. Aubin, J. Loftus, E. Beetz, I. Cussac, I. Medecin, L. Albertini

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The French version of the CTI is available on request: s.folkard@swan.ac.uk

DECLARATION OF INTEREST

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