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Joint analysis of cognitive and circadian variation in Schizophrenia and Bipolar I Disorder

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Abstract

Background—Impairment in cognitive variables and alterations in circadian function have been documented among patients with schizophrenia (SZ) and bipolar I disorder (BP1), but it is not known whether joint analysis of these variables can define clinically relevant sub-groups in either disorder.

Objectives—To evaluate the pattern and relationship of cognitive and circadian function in SZ and BP1 patients with respect to diagnosis and indices of clinical severity.

Methods—Among patients with SZ and BP1, cognitive function was evaluated using the Penn Computerized Neurocognitive Battery and circadian function was assessed using the Composite Scale of Morningness/Eveningness (CSM). Clinical severity was estimated using the Global Assessment of Function (GAF) scale, and age at onset of illness (AAO). The patients were compared with community based non-psychotic control individuals and non-psychotic first degree

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Conflict of interest

There is no conflict of interest in this manuscript.

relatives of the SZ patients. The cluster distributions of cognitive function, circadian function and clinical severity were investigated and identified clusters compared across diagnostic groups.

Results—Across participants, the cognitive domains could be separated into two clusters. Cluster 1 included the majority of control individuals and non-psychotic relatives, while SZ patients predominated in Cluster 2. BP1 patients were distributed across both clusters. The clusters could be differentiated by GAF scores, but not AAO. CSM scores were not significantly correlated with individual cognitive domains or with the clusters.

Conclusions—Clusters based on levels of cognitive function can discriminate SZ patients from control individuals, but not BP1 patients. CSM scores do not contribute to such discrimination.

Keywords

Schizophrenia; Bipolar disorder; Circadian rhythm; Cognitive function; Cluster analysis; Clinical severity

Background

Research in schizophrenia (SZ) has focused on quantifiable, heritable traits or ‘endophenotypes’ that are correlated with the diagnostic variables. Endophenotypes are measurable biomarkers that potentially provide a link between genetic contributions to a disorder and diagnosable symptoms of psychopathology (Miller, 2016). The endophenotype concept of schizophrenia represents an important approach in the exploration of the neurobiology of the illness (Tenyi et al., 2015). The endophenotypes constitute a continuum from healthy individuals, relatives of patients to patients themselves, that can discriminate between patients and controls (Antila et al., 2007a,b; Bromundt et al., 2011; Gottesman and Gould, 2003; Laurent et al., 2000). Several studies have documented differences between patients with schizophrenia, their unaffected relatives and control individuals with regard to variations in cognitive and circadian function; thus the relevant variables can be investigated as potential endophenotypes (Afonso, Viveiros, Vinhas, & de Sousa 2011; Afonso, Brissos, Canas, Bobes, & Bernardo-Fernandez, 2014; Bromundt et al., 2011; Chan et al., 2009; Mansour, Wood, & Logue, 2006; Wulff, Joyce, Middleton, Dijk, & Foster, 2006).

Impairment in several domains of cognitive function is well established in persons with SZ (Gur et al., 2007; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Silver, Feldman, Bilker, & Gur, 2003). The impairment includes working memory and attention, as well as problem solving, processing speed and social cognition (Laes and Sponheim, 2006; Nuechterlein et al., 2004; Sachs, Schaffer, & Winklbaur, 2007). Deficits in verbal memory, executive functioning, and vigilance have also been consistently documented (Bromundt et al., 2011; Green, 2006). Cognitive impairment appears to be more severe and has been observed at a younger age among patients with SZ, compared with affective disorder (Keefe, 2008). The cognitive impairments can predate the onset of SZ and can also occur among non-psychotic relatives of the patients (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Tuulio-Henriksson et al., 2003). The impairments are correlated with relatively poor outcome (Trivedi et al., 2007).

Abnormalities in circadian function and sleep have also been documented among patients with SZ, although they have not been investigated as extensively as the cognitive abnormalities (Wirz-Justice, Cajochen, & Nussbaum, 1997) (Ahn et al., 2008; Brissos et al., 2013; Martin et al., 2001; Waters and Bucks, 2011; Wulff et al., 2006). Circadian abnormalities have been observed in several variables that show circadian variation, including sleep/wake cycles, hormone levels, and levels of activity, as well as diurnal preference for daily functional activities (Afonso et al., 2014; Bunney and Bunney, 2000; McClung, 2007; Reppert and Weaver, 2001). Similarly, mood instability and disturbances of circadian rhythms have been observed more frequently among cases with bipolar disorder when compared with controls (Martin et al., 2001; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2008; Soreca, Frank, & Kupfer, 2009), though the patterns of case-control differences differ from those observed for SZ (Antila et al., 2007a; Green, 2006; Martin et al., 2001; Trivedi et al., 2008, 2007; Zalla et al., 2004). One variable by itself may not discriminate between cases and controls. Since cognitive and circadian function disturbances have been documented among patients with schizophrenia and controls, together they could provide better discrimination. Studies suggest that disruptions in circadian timing through shift work, jet lag or other processes can lead to neurobehavioral deficits, which can manifest as alteration in mood, affect or cognitive function (Karatsoreos, 2014). In occupations with high cognitive loads, disrupted circadian clocks and sleep cycles could lead to significant degradation in cognitive function. Other studies have reported on association between circadian rhythm and cognition, but not with symptoms severity and duration of illness (Wulff et al., 2006; Bromundt et al., 2011).

It is possible that sub-groups of patients with particular constellations of endophenotypes occur in both disorders, with differences in the prevalence and severity of the impairments. To our knowledge, such analyses have not been conducted, nor have simultaneous analyses of cognitive and circadian variables among patients with SZ and BP1. Moreover, studies of circadian variables as endophenotype of BP1 are more frequent than those of SZ. Therefore, we conducted cluster analysis of cognitive variables and morningness/eveningness, a stable, self-reported measure that reflects circadian phase, among patients with SZ, BP1, first degree relatives of SZ and controls. We examined whether clinically meaningful clusters could be defined when patients with SZ and BP1 were analyzed alongside two groups of controls. We evaluated age at onset of illness and global assessment of function, two widely used indices of clinical severity. These are inversely correlated with clinical severity and outcome in SZ (Bellino et al., 2004; Rajji, Ismail, & Mulsant, 2009; Ochoa, Villalta-Gil, Márquez, Valdelomar, & Haro, 2006; Van der Werf, Kohler, Verkaaik, Verhey, & Van Os, 2016) and BPD (Carlson, Bromet, Driessens, Mojtabai, & Schwartz, 2002). Several investigators have previously reported the association of age at onset (AAO) with clinical severity scores and cognition among patients with SZ and Bipolar Disorder (Afonso et al., 2014, 2011; Bellino et al., 2004) (Mansour et al., 2005; Marsh et al., 1997; Rajji et al., 2009; Tuulio-Henriksson, Partonen, Suvisaari, Haukka, & Lonnqvist, 2004; Van der Werf et al., 2016).

Methods

Design

Individuals with SZ or Bipolar I disorder (BP1) were investigated. For comparison, we evaluated individuals from the same communities of the patients as potential unrelated controls. We also included non-psychotic first degree relatives of the SZ patients as a second comparison group. We utilized three sets of variables in the analyses: cognitive function, circadian function and indices of clinical severity. Cluster analysis was used to investigate the distribution of these variables and to compare the frequency of clusters identified across the diagnostic groups.

Site

The study was conducted at the Department of Psychiatry, Centre of Excellence in Mental Health, Post-Graduate Institute of Medical Education and Research– Dr Ram Manohar Lohia Hospital (RML), New Delhi. RML is a Government of India funded teaching hospital that serves residents of the metropolitan Delhi area as well as the surrounding states free of charge.

Participants

All participants provided written informed consent, following approval of the study by the Institutional Ethics Committee of Dr Ram Manohar Lohia Hospital and the Institutional Review Board, University of Pittsburgh.

Patients

Individuals aged 18–60 years, with a clinical diagnosis of SZ or BP1 were referred by therapists at RML for further evaluation by research staff. Individuals with a history of substance abuse, mental retardation or neurological illness were excluded.

Community based controls

Individuals unrelated to the patients were recruited from the same residential areas as the patients. Participants of either gender, between 18 and 60 years of age were eligible for participation. Controls were screened for absence of a history of psychiatric illness using the Diagnostic Interview for Genetic Studies. They were also screened for family history of psychiatric illness using the Family Interview for Genetic Studies (FIGS). Individuals with a history of drug or alcohol abuse within previous 6 months or any neurological or serious medical illness that could interfere with cognitive evaluations were excluded.

Relatives of SZ patients

All first degree relatives of the SZ patients were eligible to participate, provided they were 18–60 years of age. Where possible, siblings nearest in age to the probands were recruited. Only one relative from the family of each SZ patient was included in the analysis, preferably the sibling. If no siblings were available, parents were recruited.

Assessment

Diagnostic interview for genetic studies (DIGS)—The Hindi version of the DIGS was used as the primary diagnostic interview schedule (Deshpande et al., 1998). This comprehensive semistructured interview provides current and lifetime details on demographic data, medical history and major psychiatric disorders (Nurnberger et al., 1994). It also includes standard clinical rating scales including the Global Assessment Scale, the Mini Mental State Examination, the Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms and the Operational Criteria (OPCRIT) checklist. The DIGS takes 2–3 h to complete.

Consensus diagnosis—A consensus diagnosis was assigned using DSM IV criteria by a licensed psychiatrist and psychologists following evaluation of structured diagnostic interview information, available medical records and information obtained from relatives with the participants' consent (Bhatia et al., 2006).

University of Pennsylvania computerized neurocognitive battery (Penn CNB)—Cognitive function was assessed using the Pennsylvania Computerized Neurocognitive Battery (Penn CNB) (Gur et al., 2001). The Penn CNB includes major cognitive domains impaired in SZ (Gur et al., 2007). Its psychometric properties have been evaluated (Moore, Reise, Gur, Hakonarson, & Gur, 2015; Sachs et al., 2004). The computer based tests are designed to yield quantitative measures of key cognitive domains and include a training module. The CNB is designed to yield quantitative measures of key cognitive domains. It includes a training module. It has automated scoring with direct data downloading for the following domains, including accuracy and time for completion of each module: Abstraction and mental flexibility, Attention, Face memory, Spatial memory, working memory, Spatial ability, Emotion and Sensorimotor dexterity.

To reduce the number of comparisons, only accuracy variables for each cognitive domain were utilized for analysis as accuracy and time for completion are usually correlated. All instructions were provided in Hindi and it was ensured that all participants understood the instructions clearly. The administration time for Penn CNB is approximately 2 to 2.5 h.

Composite scale of morningness/eveningness (CSM)—The CSM was used to evaluate Morningness/Eveningness (M/E), a trait that indexes diurnal preference for a set of daily activities and serves as a convenient proxy for several circadian and sleep related variables (Smith, Reilly, & Midkiff, 1989) (Greenwood, 1994). The CSM, composed of 13 items, is a validated adaptation of the Horne-Ostberg scale that is used to assess Morningness/Eveningness (M/E) (Horne and Ostberg, 1976) (Diaz-Morales, de Leon, & Sorroche, 2007) (Onder, Besoluk, & Horzum, 2013). The CSM score was regarded as a continuous variable measuring the degree of M/E. The scale was translated in to Hindi and field tested before use. Approximately 10 min were required to complete the CSM.

Indices of clinical severity—We included the Global Assessment of Function (GAF), an anchored scale that assesses level of severity with regard to clinical features and daily

function (Endicott, Spitzer, Fleiss, & Cohen, 1976). Age at onset (AAO) was the second index of severity and was evaluated only for the SZ and BP1 patients.

Statistical analysis—We initially conducted conventional demographic and clinical comparisons of the participants using univariate analyses. Regression was used to obtain age adjusted standardized residuals. Subsequently, we conducted cluster analyses to identify meaningful groups of circadian/ cognitive variables. Next, we analyzed the contributions of diagnostic groups within clusters using analyses of variance (ANOVA).

Results

There were a total of 320 participants enrolled in the study. Among these, 57 were diagnosed with BP1, 105 were diagnosed with schizophrenia, 71 were relatives of the participants with schizophrenia, and 87 were control individuals. The demographic characteristics, cognitive measures and CSM scores for each diagnostic category are summarized in Table 1. Gender was not significantly different across diagnosis (p -value = 0.38). We applied analysis of variance to test for differences in age between the four groups. We found that age was significantly different across these groups (SZ, First degree relatives of schizophrenia patients, BP1 and control) with F -value 3.897 and p - value 0.009. (Table 1). In addition, we conducted the Student's independent t -test, and found that the SZ and BP1 diagnostic groups were not significantly different for age (t = -1.588, p - value= 0.114). Post- hoc analyses of variance test using the Games-Howell method were conducted to compare ages between pairs of groups. We found that controls were significantly younger in age compared to the relatives of SZ (p - value = 0.034). No other significant differences were found.

There were significant group-wise differences for the cognitive variables, with SZ patients showing the most severe impairment in most domains, followed by the BP1 patients and the relatives of SZ patients, when analyzed in relation to the controls (Table 1). Modest differences in CSM scores were also noted, with the scores for the SZ and BP1 groups being lower than the controls or the relatives; i.e., the patients (SZ, BP1) were more likely to be evening type. Correlation matrices between the cognitive measures and the CSM scores indicated that all the cognitive measures were significantly correlated ($p < 0.0001$), but the CSM scores were not significantly correlated with any of the cognitive variables (data not shown).

Cluster analyses based on the circadian and cognitive variables indicated the presence of two clusters; their composition varied by group (Table 2). The clusters were next evaluated in relation to AAO and past month GAF scores in order to evaluate their clinical relevance (Table 3). Only the SZ and BP1 patients were included in the analyses as these variables were not meaningful for the controls or the relatives. Individuals in Cluster 1 had significantly higher GAF scores than the individuals in cluster 2 when the BP1 and SZ groups were analyzed together ($p < 0.0001$), or when the SZ and BP1 groups were analyzed separately (p = 0.03 in BP1 group and p = 0.004 in SZ group). The mean AAO did not differ significantly between the two clusters when all the patients were analyzed together or the diagnostic groups were analyzed separately.

Next, Z scores for each cognitive domain and CSM scores were compared between each cluster, separately by diagnostic group (ANOVA, Table 4). There were significant differences across clusters for each cognitive domain. As would be expected, there were no significant differences when cognitive domains were analyzed across diagnostic groups within each cluster except cluster 2 working memory where nominal difference was found. In contrast, CSM scores were not significantly different between clusters in any of the diagnostic groups, or in the entire sample (results not shown). There were non-significant trends for differences across clusters for the SZ and controls.

Discussion

Two distinct clusters could be identified based on the cognitive domains across all four groups of individuals in the present study. Cluster 1 broadly encompassed individuals with higher levels of cognitive function and included the majority of the controls and the non-psychotic relatives. Cluster 2, on the other hand discriminated the SZ group from the non-psychotic individuals. The BP1 patients were distributed in both clusters. The clusters also varied in relation to GAF scores. These results are consistent with prior publications (Gur et al., 2007; Sachs et al., 2004; Trivedi et al., 2007; Zalla et al., 2004). Our analyses indicate that addition of CSM scores to the cognitive variables did not enable further discrimination in the samples. Similar to the initial analyses with only the cognitive variables, the controls formed relatively homogenous, orthogonal clusters incorporating CNB domains and the CSM. The relative proportions of these clusters differed among patients with SZ and BP1, with SZ patients predominating in cluster 2, and the BP1 patients were represented in both clusters. The prevalence of these clusters differed significantly between the SZ and BP1 groups.

Some important limitations of the study should be kept in mind. Medication status was not included in the analyses. Intelligence is another important, relevant variable for the present study. Though a few puzzles from Raven's Progressive Matrices are included in the CNB, intelligence scores could not be calculated.

In conclusion, cluster analysis of cognitive variation indicated two clusters. The cluster analysis enabled clear discrimination of patients with SZ from control, but similar discrimination was not attained for the BP1 patients. The clusters appeared to be related to clinical severity as estimated using AAO. Additional clusters were not identifiable when CSM scores were added to the cognitive variables.

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Table 1

Demographic, cognitive and CSM measures in the diagnostic groups using ANOVA.

	BP1 (n = 57)	SZ (n = 105)	SZ_rel (n = 71)	Control (n = 87)	*p-value	#p-value
Men, n (%)	34 (60)	66 (63)	52 (73)	56 (64)	0.38	0.69
Age, mean (SD)	34.88(12.47)	32.17 (9.01)	36.28 (14.79)	30.70 (9.51)	0.009	0.114
Abstraction and mental flexibility	-1.37 (0.89)	-1.47 (0.83)	-1.03 (0.80)	-0.74 (0.90)	<0.0001	0.32
Face Memory	-0.50 (1.58)	-0.51 (1.38)	0.25 (1.10)	0.29 (1.21)	<0.0001	0.69
Spatial Memory	-0.70 (1.08)	-0.62 (0.96)	-0.07 (1.00)	0.04 (1.06)	<0.0001	0.75
Working Memory	-1.32 (1.25)	-1.58 (1.43)	-0.50 (0.88)	-0.47 (1.11)	<0.0001	0.36
Sensorimotor function	0.13 (0.99)	-0.08 (1.14)	0.24 (0.90)	0.51 (0.66)	<0.0001	0.56
Emotion Processing	-0.69 (0.88)	-0.81 (0.90)	-0.48 (0.89)	-0.22 (0.82)	<0.0001	0.40
Composite scale of morningness	42.12 (5.66)	41.31 (6.17)	43.51 (5.59)	43.55 (5.32)	0.02	0.36

BP1: bipolar I disorder, SZ: schizophrenia, SZ_rel: relatives of patients with SZ, control: individuals without psychosis.

* p- value from Analysis of variance (BP1, SZ, SZ_Rel and Controls were compared).

p- value for student's *t*-test (BP1 and SZ groups compared).

Table 2

Distribution of clusters by diagnostic group.

Group	Cluster 1 n (row, column%)	Cluster 2 n (row%, column%)	Total
BP1	28 (49.12, 14.58)	29 (50.88, 22.66)	57
SZ	39 (37.14, 20.31)	66 (62.86, 51.56)	105
SZ_relative	54 (76.06, 28.13)	17 (23.94, 13.28)	71
Control	71 (81.61, 36.98)	16 (18.39, 12.50)	87
Total	192	128	320

BP1: Bipolar I disorder. SZ: schizophrenia. SZ_rel: relatives of patients with SZ, control: individuals without psychosis. In each cell, variables are listed in the following order: frequency, row% and column%.

Table 3

Indices of clinical severity by cluster among BP1 and SZ patients.

Diagnosis	Indices of clinical severity	Cluster 1	Cluster 2	p-value *
		Mean (SD, n)	Mean (SD, n)	
BP1 + SZ	AAO	26.3 (7.3, 63)	25.8 (8.6, 95)	0.69
	GAF	42.2 (15.7, 66)	33.4 (15.7, 94)	0.0001
BP1	AAO	28.2 (9.1, 25)	25.1 (8.5, 29)	0.20
	GAF	47.9 (17.7, 28)	38.2 (15.5, 29)	0.03
SZ	AAO	25.1 (5.6, 38)	26.1 (8.7, 66)	0.48
	GAF	38.2 (12.9, 38)	31.3 (10.6, 65)	0.004

BP1: Bipolar I disorder. SZ: schizophrenia. AAO: Age at onset of illness. GAF: global assessment of functioning scores (past month). Values listed as mean (SD, n) in each cell.

* p- value from *t*-test.

Table 4
Analysis of cognitive measures and Composite scale of morningness scores within and across clusters.

		BPI	SZ	SZ_Rel	Control	p-value*
Abstraction and mental flexibility	Cluster 1	0.4015	0.4107	0.4326	0.6304	0.39
	Cluster 2	-0.8462	-0.8551	-0.7089	-0.56619	0.41
	p-value#	< 0.0001	< 0.0001	< 0.0001	< 0.0001	
Face Memory	Cluster 1	0.3164	0.4029	0.4975	0.4475	0.85
	Cluster 2	-0.8178	-0.809	-0.3477	-0.7147	0.07
	p-value#	< 0.0001	< 0.0001	0.0002	< 0.0001	
Spatial Memory	Cluster 1	-0.235	0.2728	0.4635	0.5129	0.43
	Cluster 2	-0.9006	-0.6811	-0.4552	-0.6895	0.17
	p-value#	< 0.0001	< 0.0001	0.0007	< 0.0001	
Working Memory	Cluster 1	-0.4026	0.2531	0.5285	0.5825	0.09
	Cluster 2	-0.826	-0.9057	-0.1008	-0.5499	0.02
	p-value#	< 0.0001	< 0.0001	0.0006	< 0.0001	
Sensorimotor Dexterity	Cluster 1	-0.3852	0.429	0.3086	0.3957	0.6
	Cluster 2	-0.492	-0.7907	-0.5602	-0.3289	0.53
	p-value#	0.001	< 0.0001	0.0001	0.0002	
Emotion Processing	Cluster 1	-0.3694	0.4149	0.4457	0.4825	0.92
	Cluster 2	-0.6754	-0.7755	-1.0443	-0.4606	0.27
	p-value#	< 0.0001	< 0.0001	< 0.0001	< 0.0001	
Composite scale of morningness	Cluster 1	-0.1961	-0.4527	0.02853	0.12617	0.02
	Cluster 2	-0.0721	-0.0727	0.23554	0.59249	0.08
	p-value#	0.63	0.08	0.43	0.06	

BPI: Bipolar I disorder. SZ: schizophrenia. SZ_rel: relatives of patients with SZ. control: individuals without psychosis.

* Denotes p-value for comparison of z scores for diagnostic groups within that cluster.

Denotes p-value for comparison of z scores for diagnostic groups between clusters.