Associations between cognitive impairment and P300 mean amplitudes in individuals with bipolar disorder in remission

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ABSTRACT

Cognitive functions are often affected during the euthymic state of bipolar disorder (BD). In this study, we investigated the associations among cognitive complaints, objective cognitive functions, and the mean amplitudes of the P300 event-related potential (ERP) wave in individuals with BD. The study population comprised 33 individuals with BD who were in remission and was conducted at Hokkaido University Hospital, Sapporo, Japan. Cognitive complaints were assessed using the Japanese version of the tool named “cognitive complaints in bipolar disorder rating assessment (COBRA)”, whereas objective cognitive functions were measured by neuropsychological tests. P300 mean amplitudes were investigated during two- and three-stimulus oddball tasks and showed significant correlations with neuropsychological test scores at all electrode locations, confirming that ERPs and objective cognitive tests that assessed attention and memory function tend to coincide; however, neither P300 amplitudes nor neuropsychological test scores were correlated with COBRA scores. ERPs most likely represent the neurophysiological basis for objective rather than subjective cognitive function in euthymic individuals. Thus, our results suggest that objective cognitive function is related more to P300 mean amplitude scores than subjective cognitive function in individuals with BD.

Keywords: cognitive complaints, cognitive function, neuropsychological assessment, euthymia

1. Introduction

Individuals with bipolar disorder (BD) experience both recurring manic and depressive episodes as defined by the *Diagnostic and Statistical Manual of Psychiatric Disorders, Fifth Edition* (DSM-5) (American Psychiatric Association, 2013). During both phases of these episodes, individuals can exhibit a variety of cognitive dysfunctions (Martínez-Arán et al., 2004a; Porter et al., 2015) that have been attributed to altered mood (Basso et al., 2002; Glahn et al., 2007). Those individuals in remission (i.e., the euthymic phase) will continue to show cognitive impairments that affect mainly memory, attention, and executive function (Basso et al., 2002; Joe et al., 2008; Martínez-Arán et al. 2004b; Sumiyoshi et al., 2017). This suggests that cognitive impairments do not result from only mood changes but rather reflect neurobiological changes (Vieta et al., 2018).

Quality of life (QOL) and functional recovery are important new treatment targets for BD individuals (Miskowiak et al., 2018). Persistent cognitive dysfunction during the euthymic phases are directly related to an individual's poor QOL (Mackala et al., 2014). The association between cognitive impairment and QOL in euthymic BD individuals was also reported, and subjective cognitive function is related more to QOL than objective cognitive function (Toyoshima et al., 2018). For example, individuals make mistakes because of poor attention, which results in their inability to apply their talent or abilities that qualify them for the job, even during euthymic phases.

Various instruments that assess neurocognitive functions are available and can be classified into subjective and objective assessment tools (Demant et al., 2015; Jensen et al., 2015). A self-report instrument called the "cognitive complaints in bipolar disorder rating assessment (COBRA)" was recently developed specifically for individuals with BD (Rosa et al., 2013). Subjective impairments should be assessed routinely in these individuals according to the International Society for Bipolar Disorders (ISBD) Targeting Cognition Task

Force (Miskowiak et al., 2017), and COBRA, in addition to objective neuropsychological assessments, is recommended for such screening. ISBD recommends assessing both objective and subjective cognition because it is not always the individuals with the most subjective complaints who show greatest objective impairments and vice versa. COBRA is a subjective cognitive-screening tool that is brief, easy, and cost effective for both clinicians and individuals (Miskowiak et al., 2018).

Event-related potentials (ERPs) have high temporal resolution that allow for different electrophysiological components to be observed, and represent distinct cognitive stages that occur during a task (Nunez, 1981). ERP components might index specific pathophysiological mechanisms that may or may not recover with remission of an illness (Morsel et al., 2018).

The mean ERP P300 amplitude was used as a neurobiological indicator for cognitive function in our study and was assessed during two oddball paradigms—a two-stimulus and three-stimulus task. In the auditory two-stimulus oddball paradigm, two distinguishable stimuli (e.g., treble vs. bass) were presented in random order and with a different presentation frequency for each type (e.g., treble at 20% vs. bass at 80%). The participating individuals responded by pressing a button only when the infrequent target stimulus was presented. The frequent stimulus is usually referred to as "standard" or "nontarget" stimulus. The P300 for the target stimulus appears with higher amplitudes at the midline (Cz) and parietal locations (Pz) at ~300 ms after the onset of the stimulation. The three-stimulus oddball paradigm comprised an additional infrequent new stimulus (e.g., white noise). In this paradigm, the individual was asked to react to the target stimulus and ignore the new stimulus. The P300 here revealed two components—an earlier peak called "P3a" for the new stimulus that appeared predominantly at the frontal (Fz) and central (Cz) electrodes (Comerchero and Polich, 1999; Squires et al., 1975), and the regular P300 for the target stimulus, referred to as "P3b", that occurred after P3a and was usually larger over the Pz region. P3a is interpreted as an index for the orienting response (novelty detection) that demands frontal attention, while P3b is interpreted as an attentional resource allocated for updating working memory (Polich and Criado, 2006).

Many studies have demonstrated reduced P300 amplitudes, especially P3b amplitudes, in individuals with BD, including those in the euthymic phase (Morsel et al., 2018), while P3a appears to be less affected. Our current study was thus aimed specifically at examining the relationships among subjective cognitive function, objective cognitive function, and the mean amplitudes of the P300 during two different oddball tasks. The amplitudes were compared to both subjective and objective cognitive impairments in a group of individuals during the euthymic phase of their BD. The main hypothesis was that objective cognitive dysfunction could be reflected in reduced P300 amplitudes, particularly in reduced P3b amplitudes. Furthermore, cognitive disturbances might differ between disorder subtypes—BD I individuals have manic episodes and BD II individuals have hypomanic episodes—; however, little is known about whether P300 amplitudes differ between individuals of subtypes BD I or BD II. The current study thus compared cognitive functions and ERPs in individuals of each subtype.

2. Methods

2.1. Participants

In total, 33 participants were enrolled in the study using convenience sampling between November 2014 and February 2016 at Hokkaido University Hospital, Sapporo, Japan. These individuals satisfied the DSM-5 full remission criteria, and ≤7 points for at least 8 weeks before the assessment on both the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Hamilton Rating Scale for Depression (17-HAM-D) (Hamilton, 1960). Using the DSM-5 criteria, an attending psychiatrist diagnosed subtype BD I in 10 individuals and subtype BD II in 23. Other inclusion criteria were as follows: 1) outpatient at the Department of Psychiatry, Hokkaido University Hospital, and 2) individuals were 18–64 years old. The exclusion criteria were as follows: 1) inpatient with intellectual disability, 2) unstable medical illness, 3) history of moderate to severe brain injury, 4) present uncontrolled thyroid condition, 5) neurological disease, 6) present or recent alcohol and substance use disorder, or 7) current comorbid diagnosis of attention deficit hyperactivity disorder. The local Ethics Committee of Hokkaido University (Ethics Approval Number: 014-0006) approved the study. The study rationale and procedures were fully explained to all individuals, and all gave their written informed consent.

2.2. Assessments

All 33 individuals underwent the COBRA neuropsychological assessment, and ERP measurements were conducted. The study duration for each participant was approximately 180–210 min, which included regular breaks.

2.2.1. Sociodemographic and clinical assessment

Table 1 shows clinical and sociodemographic data collated from the hospital's electronic patient records. Table 2 shows the medication information for each participant; however, this information was not used as a control parameter. YMRS and 17-HAM-D were used to assess manic and depressive symptoms, respectively, through clinical assessments. The Japanese Adult Reading Test (abridged version, JART-25) and the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006) were used to assess intelligence.

2.2.2. Subjective cognitive function

COBRA, a 16-item self-report questionnaire (Rosa et al., 2013; Toyoshima et al., 2017; Toyoshima et al., 2018), was used to assess subjective cognitive function. COBRA is scored on a 4-point scale (0 = never, 1 = sometimes, 2 = often, 3 = always). Questions were related to everyday mental abilities (e.g., concentration problems while reading or remembering names, or word-finding difficulties). The total COBRA score is the sum of the scores for each individual item. The maximum score is 48 and the minimum is 0. The higher the scores, the worse were the subjective complaints.

2.2.3 Neuropsychological assessment

The following items from the module for determining cognitive function at Hokkaido University Hospital Department of Psychiatry were used to assess neuropsychological functions (Toyomaki et al., 2008; Toyomaki et al., 2015): 1) JART-25 (Matsuoka et al., 2006) estimates the individual's pre-illness intelligence quotient; 2) the Wisconsin Card Sorting Test (WCST, Keio version) (Kashima and Kato, 1995) evaluates the number of achieved categories (WCSTCA) and perseverative errors (Milner type) as indicators for executive function; 3) the Word Fluency Test (WFT) assesses executive control, such as asking individuals to produce nouns that begin with a specific character (e.g., "し [shi]," "い [i]," and "れ [re]"; 1 min for each character) (Toyomaki et al., 2015); 4) the Continuous Performance Test (CPT) uses a stimulus presentation software (A-X CPT, 7 min) (Rosvold et al., 1956) to assess sustained attention and reaction times (RT) (Toyomaki et al., 2015); 5) the Trail Making Test (TMTA, connecting sequences of numerals, 1-2-3, etc., and TMTB, connecting sequences alternating between numerals and letters, 1-A-2-B, etc.) (Reitan, 1958) assesses visual processing, executive function, and movement speed; 6) the Auditory Verbal Learning Test (AVLT) (Yamashima et al., 2002) presents 10 words that required immediate (i) and recent (r, after 30 min) recall; and 7) the Stroop Test (ST) described previously (Toyoshima et al, 2018) assesses response suppression and selective attention. For comparison, data of 78 healthy subjects in our facility are shown in Table 3.

2.2.4. P300 mean amplitude of event-related potentials

Two- and a three-stimulus oddball tasks were implemented, with a target stimulus occurring less frequently than the standard stimulus. The distractor in the three-stimulus oddball task also occurs infrequently and is more prominent than the other two. In the current study, the standard (1000 Hz), target (2000 Hz), and new stimuli (environmental sound) were presented for 70 ms each with a variable interstimulus interval of 950–1550 ms. The presentation frequency of the target stimulus was 20% in the two-stimulus and 15% in the three-stimulus tasks, while the frequency of the distractor was 15%. The participants were instructed to respond only when the target stimulus was presented. They completed two sets of 125 trials (i.e., 125 stimuli) of the two-stimulus and 160 trials of the three-stimulus tasks.

Electroencephalogram (EEG) signals (bandpass, 0.16–30 Hz; digitized at 500 Hz) were recorded from three electrodes (Fz, Cz, and Pz) as per the international 10/20 system using the Neurofax 1100 digital EEG (Nihon Kohden Corp., Tokyo, Japan). Ag/AgCl electrodes were used with impedance kept at <10 kΩ and referenced to the earlobes. Eye movements were monitored using electrooculograms (EOGs) recorded from electrodes lateral to and below the left eye. P300 amplitude was defined as the peak-to-peak difference in μV between the average baseline voltage and the largest positive ERP peak from the preceding negative trough between 250 and 500 ms after the onset of the stimulus. Within this temporal window, the P3a component was defined as the earlier larger peak elicited by the distractor, and the P3b as the later smaller peak evoked by the target stimulus (Polich, 2007). We set the time windows of the P300 mean amplitude measurement component as follows: two-tone P3b, three-tone P3a, and three-tone P3b were 306–356, 336–386, and 344–394 ms, respectively.

2.3. Statistical analyses

Spearman correlations were computed among the P300 amplitudes at Fz, Cz, and Pz during the two- and three-stimulus oddball tasks (t2 and t3, respectively) and the cognitive assessments (COBRA, neuropsychological tests). SPSS v. 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses, and $p < 0.05$ was considered statistically significant.

For basic comparisons relating to the mean P300 amplitude, individuals were grouped based on their illness diagnosis (BD I, $n = 10$; BD II, $n = 23$) to compare the wave amplitude to the COBRA scores, and then categorized into two groups based on a cutoff score (low, ≤14, $n = 18$; high, >14, $n = 15$) (Miskowiak et al., 2018). Comparisons between the groups were conducted using the Mann-Whitney *U* test for analyses of nonparametric data.

3. Results

3.1. Basic findings

Table 1 shows the clinical and sociodemographic characteristics of the 33 individuals. The group comprised a larger percentage of females that males, and the majority of the conditions were diagnosed as the BD II subtype. The average COBRA score was 14.18 ± 7.75, which was lower than that reported in previous studies (Jensen et al., 2015; Rosa et al., 2013).

The average scores from the various neuropsychological tests are summarized in Table 3. Processing speed (TMTA, TMTB, STRT) and error monitoring (STerr, CPTerr), were strongly impaired, while immediate and delayed recall (AVLTi, AVLTr) were only moderately impaired.

The COBRA scores did not differ significantly between individuals of subtypes BD I and BD II (Mann-Whitney *U* test). WCSTCA ($Z = -2.461$, $p = 0.014$) and STerr ($Z = -2.582$, $p = 0.010$) yielded significant differences between subtypes; individuals of the BD I subtype completed more categories in WCST but also made more errors in ST.

P300 amplitudes were compared at three electrode sites between the two subtypes, which differed significantly in P3b at only the Cz electrode during both oddball tasks (two-tone, $Z = -2.468$, $p = 0.014$; three-tone, $Z = -1.998$, $p = 0.046$). Individuals of the BD I subtype showed higher amplitudes at this central location during both tasks.

3.2. Associations of subjective cognitive function with neuropsychological tests and P300 amplitudes

The correlation analyses indicated that the total COBRA score was not significantly correlated with any of the neuropsychological tests (Supplementary Table S1). Furthermore, none of the neuropsychological tests showed significant differences between the high and low COBRA score groups, and the total COBRA score was not significantly correlated with any of the P300 mean amplitudes (Supplementary Table S2). These negative findings were confirmed by observing that individual P300 mean amplitudes did not differ in either the high- or low-score COBRA group.

3.3. Associations between objective cognitive functions and P300 mean amplitudes

Several correlations between neuropsychological tests and P300 mean amplitudes were significant (Supplementary Table S3): STerr was positively correlated with P3b at Cz (*rho* =.445, *p* =.009) during the two-tone oddball task and with P3b at Fz (*rho* =.355, *p* =.043) and Cz (*rho* =.421, *p* =.015) during the three-tone oddball task. This suggests that the P300 amplitudes increased when individuals made more errors in the ST color-naming task. AVLTr was positively correlated with P3b at the parietal electrode (Pz) during the two-tone oddball task (*rho* =.359, *p* =.04) and with P3a during the three-tone oddball task (*rho* =.369, *p* =.035); therefore, better performance during delayed recall was associated with higher P300 amplitudes over the parietal regions.

3.4. Associations among subjective cognitive functions and sociodemographic and clinical characteristics

None of the correlations among subjective cognitive functions and sociodemographic and clinical characteristics were significant (Supplementary Table S4).

4. Discussion

The main aim of this study was to examine associations among subjective cognitive impairments (COBRA; Toyoshima et al., 2017), objective cognitive functions, and P300 mean amplitudes during the two-tone and three-tone oddball task in individuals with BD that was in remission.

Subjective cognitive impairments did not correlate with neuropsychological test results, which matched the results of previous reports (Miskowiak et al., 2016; Miskowiak et al., 2017; Toyoshima et al., 2018). This was further supported by the current new finding that subjective cognitive dysfunction was not associated with P300 amplitudes. Not only objective cognitive function but also P300 amplitudes can be affected by residual mood symptoms; however, these could more strongly contribute to subjective cognitive complaints. In addition, another confounding factor, such as a history of psychosis and medication, could separately contribute to subjective cognitive function, objective cognitive function, and P300 amplitudes. Thus, what euthymic individuals subjectively experience as cognitive impairment does not necessarily manifest in objective cognitive or neurophysiological measurements, as shown by the P300 amplitudes; however, two neuropsychological functions—selective attention (STerr) and memory (delayed recall)—showed significant associations with amplitudes of both P300 components over central, parietal, and frontal regions. Higher error rates during the ST task representing reduced inhibitory control (Bora et al., 2013) were associated with higher P3b amplitudes over central and frontal areas. P3a and P3b can result from inhibitory mechanisms (Polich and Criado, 2006), and their higher amplitude could reflect greater attentional effort from the individuals; however, this was insufficient in suppressing the incorrect response during color naming. Higher P3a and P3b amplitudes over parietal areas were related to less-delayed recall, which could indicate that the increased attentional effort contributed to improved memory performance (Polich, 2007).

As (Morsel et al. 2018) have proposed, relating cognitive functions with specific ERP components confirms that individuals during the euthymic state of BD indeed suffer from impairments in various cognitive domains that might be related to their underlying pathophysiology. This finding has implications for further treatment that should also target cognitive functions. For example, these treatments might include neuromodulation, such as transcranial magnetic stimulation (Myczkowski et al., 2018) or cognitive training.

Comparisons between individuals of subtypes BD I and BD II have yielded results that are inconsistent with ERPs (Morsel et al., 2018) and neuropsychological measurements (Miskowiak et al., 2016). Lower P3b amplitudes were documented in individuals with BD disorder compared to that in the healthy controls (Bersani et al., 2015). This study also suggests lower mean amplitudes for Cz and Fz in individuals of subtype BD II, but these differences were not significant. The current study yielded lower P3b amplitudes at the Cz electrode in individuals of subtype BD II, but the small sample size precludes further interpretation of these findings.

A recent study has reported that high-frequency repetitive transcranial magnetic stimulation (rTMS) improves neurocognitive function in individuals with BD that is in remission (Yang et al., 2019), and we suggest that interventional strategy of neuromodulation using brain stimulation, such as rTMS, for ERP-oriented cognitive rehabilitation might be possible. According to the results of this research, a multidimensional understanding of cognitive function could enable personalized medicine. In addition, in considering functional recovery strategies for individuals with BD, it might be possible to consider treatments hierarchically from a biological to a subjective level.

P300 amplitudes were used to assess objective cognitive dysfunction; however, the results of the study demonstrate that they do not reflect subjective complaints. This is critically important because subjective cognitive complaints have been shown to additionally affect the QOL of individuals with bipolar disorder (Toyoshima et al., 2018). Therefore, even when objective cognitive dysfunction is mild, if subjective cognitive dysfunction is severe, it is necessary to promptly deal with it. Therefore, COBRA is a useful tool for screening cognitive impairment associated with QOL. In addition, subjective cognitive impairments remain an important treatment target in BD to improve the functional outcome of the individuals.

4.1. Conclusions

Objective and subjective cognitive dysfunctions and their neurophysiological foundations have been documented in individuals with BP during euthymia. In this study, the association between subjective cognitive function and P300 mean amplitudes was not significant; however, some objective cognitive functions, such as attention and memory, were significantly associated with those amplitudes. Even during remission, multifaceted assessment might enable new therapeutic strategies for functional recovery in individuals with BD.

4.2. Study Limitations

This was an investigative study; therefore, no corrections for multiple comparisons were made. The study comprised a small sample size, and there was no control for several important factors, such as sociodemographic characteristics, subsyndromal symptoms, or medication (Vieta et al., 2018). The relatively modest sample size might have limited the power to detect moderate-level associations. In particular, the various pharmacological interventions that affect neurotransmitter (e.g., dopamine and catecholamines) responsivity could alter ERP characteristics (Polich, 2007). Although several correlations proved to be significant, causal interpretation of these relationships was not possible. Longitudinal studies with larger populations and stricter control of confounding variables are needed to ascertain the associations among COBRA scores, objective neuropsychological functions, and P300 mean amplitudes. In addition, the lack of a control group for subjective cognitive function and electrophysiological abnormalities was a limitation. The level of these abnormalities and their variances can influence the correlations among them. Further comparisons using individuals with other psychiatric disorders are necessary to substantiate correlation patterns.

Declarations of Interest

None.

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Tables

Table 1. Sociodemographic and clinical characteristics

Participating Individuals (*n* = 33)	Mean (SD), *n* (%)
IQ (JART-25), mean (SD)	105.48 (10.91)
Duration of illness, mean (SD)	14.85 (8.00)
Age, mean (SD)	42.82 (10.39)
Age at onset, mean (SD)	28.15 (9.41)
Male sex, *n* (%)	12 (36.4)
Years of education, mean (SD)	14.27 (2.25)
Currently employed, *n* (%)	11 (33.3)
Married, *n* (%)	16 (48.5)
Living alone, *n* (%)	9 (27.3)
Depressive onset, mean (SD)	27.36 (11.20)
Bipolar I disorder, *n* (%)	10 (30.3)
Number of hospitalizations, mean (SD)	1.79 (2.37)
Number of total episodes, mean (SD)	6.03 (4.00)
Number of hypomanic episodes, mean (SD)	1.76 (2.06)
Number of manic episodes, mean (SD)	0.73 (1.35)
Number of depressive episodes, mean (SD)	3.21 (1.73)
Number of mixed episodes, mean (SD)	0.33 (0.60)
Number of suicide attempts, mean (SD)	0.55 (0.97)
17-HAM-D score, mean (SD)	2.36 (2.32)
YMRS score, mean (SD)	0.27 (0.98)

Abbreviations: JART-25, Japanese Adult Reading Scale-25-word version; 17-HAM-D, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale

Table 2. Medications (*n* = 33)

Medication name/class	Average (mg)	SD (mg)
Li	327.27	353.79
VPA	278.79	444.24
CBZ	22.73	96.09
LTG	112.88	147.12
CP conversion	190.85	226.81
IMP conversion	13.64	34.85
DZP conversion (anxiolytic)	7.57	16.16
Total DZP conversion (anxiolytic and hypnotic)	12.82	17.02

Abbreviations: Li, lithium; VPA, valproate; CBZ, carbamazepine; LTG, lamotrigine; CP, chlorpromazine; IMP, imipramine; DZP diazepam

Table 3. Neuropsychological test scores

	Individuals	(*n* = 33)	HC	(*n* = 78)
	Average	SD	Average	SD
WCSTCA	3.91	1.89	5.72	0.53
WCSTPEM	4.06	6.12	0.45	0.77
CPTerr	3.61	3.76	1.53	1.53
CPTRT	404.41	81.02	367.52	61.44
WFT	28.97	11.00	36.91	7.76
STRT	10.03	6.57	5.65	2.98
STerr	1.06	1.39	0.27	0.73
TMTA	92.39	40.47	59.21	13.27
TMTB	108.67	53.00	63.96	17.27
AVLTi	5.21	1.39	6.32	1.63
AVLTr	6.85	2.09	8.44	1.65

Abbreviations: HC, healthy controls; WCST, Wisconsin Card Sorting Test (CA, categories achieved; PEM, perseverative errors Milner type); CPT, Continuous Performance Test (err, number of errors; RT, reaction time); WFT, Word Fluency Test; ST, Stroop test; TMTA, Trail Making Test numeric sequence; TMTB, Trail Making Test alternating numeric and alphabetic sequence; AVLT, Auditory Verbal Learning Test (i, immediate recall; r, recent recall)