Research article Ερευνητική εργασία

Hypothalamus-pituitary-adrenal (HPA) axis parameters and neurocognitive evaluation in patients with bipolar disorder*

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Bipolar disorder is associated with neurocognitive impairment but the etiology of such impairment remains largely unknown. The present study aimed at investigating the performance of bipolar patients in various neuropsychological tasks within the framework of HPA axis hyperactivity model and also the impact of disease characteristics on neuropsychological functioning. Cognitive performance of 60 bipolar-I patients and 30 healthy controls was evaluated by using tasks from the CANTAB battery targeting visual memory, executive function and inhibitory control. Current symptoms were evaluated via administration of the Hamilton Depression Rating Scale (HAMD) and Young Mania Rating Scale (YMRS) whereas assessment of functioning was performed with the Global Assessment of Functioning (GAF). Basal cortisol levels were determined and all patients were administered the Dexamethasone Suppression Test (DST). Statistically significant differences between patients and controls were found in visuo-spatial associative learning and memory, planning, attentional set shifting and inhibitory control. Worse performance in visuospatial associative memory correlated with longer duration of illness and higher levels of basal cortisol. Poorer attentional set shifting was related to higher number of manic episodes. We found no relationship of neurocognitive measures with DST suppression status, current symptom severity or history of psychosis. The results of our study confirm the presence of cognitive deficits in bipolar disorder and provide evidence on the relation of cortisol with neuropsychological functioning, especially visuo-spatial associative memory. Moreover, we have found that number of previous manic episodes and duration of illness is associated with worse cognitive performance. It is known that neurocognitive deficits are evident in many patients with bipolar disorder. These deficits are often a cause of considerable distress and can lead to impairment of psychosocial and occupational functioning. The role of HPA axis needs to be further examined in bipolar disorder. Nevertheless, the identification of factors affecting neurocognitive functioning, like basal cortisol and number of manic episodes, may contribute to the implementation of more appropriate prevention strategies.

Key words: Bipolar disorder, HPA axis, cortisol, neurocognitive functioning, visual memory, executive function.

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Introduction

Bipolar disorder (BD) is a recurrent psychiatric condition characterized by episodes of altered mood (depressive, hypomanic/manic, mixed) interspersed by periods of symptomatic remission or euthymia. Evidence has accumulated over the past decade that many, but not all, bipolar patients show significant deficits in various cognitive domains. Impairments in sustained attention, verbal memory and executive functions represent the most replicated findings during the active phases of the disease but also in euthymia.^{1,2}

The etiology of cognitive impairment in bipolar disorder remains largely unknown. Previous research has speculated that Hypothalamus-Pituitary-Adrenal (HPA) axis dysregulation may be contributing to the development of cognitive impairment.^{3,4} In fact, many bipolar patients exhibit markers of HPA axis hyperactivity, such as hypercortisolemia, increased rates of non suppression at the Dexamethasone Suppression Test (DST) or at the more sensitive combined dexamethasone suppression/corticotropin-releasing hormone stimulation test (DEX/CRH test).^{5,6} On the other hand, there is evidence for cortisol-dependent memory impairment⁷⁻⁹ and executive dysfunction⁹ in recurrent major depression, as well as in healthy subjects.^{10,11}

There have been only three studies so far investigating the association between indices of HPA axis activity and cognitive functioning in bipolar disorder but results have been inconsistent.¹²⁻¹⁴

Therefore, the present study aimed at investigating the performance of bipolar patients in various cognitive tasks targeting attention, visual memory and executive function within the framework of the HPA axis hyperactivity model. It also examined the impact of various disease-related factors suggested in the literature (such as age of onset, duration of illness, presence of affective symptoms, number of affective episodes, history of psychosis) on neuropsychological functioning. Our main hypothesis was that an increased HPA axis activity would be associated with poor cognitive performance, especially in memory and executive function tasks. We also expected to find a relationship between clinical variables indicating illness severity and cognitive dysfunction.

Material and method

Subjects

Sixty bipolar patients were consecutively recruited in the study from the 2nd Department of Psychiatry of Athens University Medical School at Attikon General Hospital during the period May 2008 – November 2009. All patients had a bipolar disorder type I diagnosis according to the DSM-IV criteria (American Psychiatric Association, 2000) and they were either attending the outpatient clinic or were admitted in the psychiatric inpatient unit. Outpatients were all euthymic, whereas inpatients were assessed close to their discharge after having responded to treatment while being at least partially remitted. Patients were excluded if they had any other current Axis I diagnosis or a serious neurological or medical condition as well as a history of substance or alcohol misuse in the past 6 months.

Thirty healthy controls with no psychiatric history matched for age and education were also included in the study. Exclusion criteria for controls were the same as for the patients. Every participant signed an informed consent form following detailed description of the study. The study was approved by the Ethics Committee of Attikon General Hospital.

Clinical assessment

Current and lifetime diagnostic status was confirmed with the Mini International Neuropsychiatric Interview.¹⁵ Presence of dementia was excluded by the administration of the Mini Mental State Examination questionnaire.¹⁶ Demographic data included age, gender, years of education, current and best-ever employment and marital status. Clinical assessment and symptom evaluation took place on the same day of cognitive testing via administration of the 17-item Hamilton Depression Rating Scale (HAMD-17)¹⁷ and Young Mania Rating Scale (YMRS).¹⁸ The cut-off point for depression was a HAMD17 total score ≥ 17 and YMRS total score ≤ 12 whereas for mania a YMRS total score ≥ 20 . Information about patients' past psychiatric history, current treatment, age at onset, duration of illness, number and type of previous episodes and history of psychotic symptoms, was collected from the patients, primary caregivers and medical records.

Neuropsychological assessment

Patients were administered a series of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) which is a computer-administrated set of tasks developed to assess specific components of cognition, especially those associated with frontal and medial temporal regions of the brain.¹⁹ The tasks were given by the same qualified psychiatrist and in the same order to all participants.

Visuo-spatial memory and learning assessment

Spatial Recognition Memory (SRM): This memory task assesses the ability to remember the spatial location of visual stimuli. Five squares are presented in sequence at different locations on the screen, and then subjects are presented a pair of squares and asked to identify which is at a location where a square was previously presented. Percentage of correct responses is recorded.

Paired Associate Learning (PAL): This visuospatial memory task requires subjects to learn the location of specific visual patterns. Designs are presented in boxes on the screen at varying locations. The designs are then presented sequentially in the centre of the screen and subjects are instructed to indicate the box in which each design was initially presented. The task involves sequential stages of increasing difficulty. The total number of errors adjusted for the number of stages successfully completed ("total errors adjusted") is recorded.

Executive function assessment

Stockings of Cambridge (SOC): This executive function task investigates the ability of planning and problem solving. It is a modified version of the well-known Tower of London task and requires subjects to rearrange coloured balls in vertical columns to match a desired final arrangement in a specified minimum number of moves. Subjects are told to plan their sequence of moves before starting to move the balls shown on the monitor. The "total problems solved in minimum moves" variable is recorded as the basic measure of the subject's planning ability.

Intradimensional/Extradimensional Attentional Set Shifting (ID/ED): This test involves sequential stages of increasing difficulty and was designed to examine component executive function processes (rule discovery and reversal) evaluated in aggregate by the

Wisconsin Card Sorting Test (WCST). It assesses the ability to maintain attention to different examples within a stimulus dimension and the ability to shift attention to a previously irrelevant stimulus dimension. The number of stages completed as well as the number of errors committed (adjusted for the number of stages successfully completed) are recorded.

Inhibitory control assessment

Stop Signal Test (SST): This is a test of response inhibition, a key dimension of executive function and gives a measure of an individual's ability to inhibit a prepotent response. Subjects are required to press the left or right button when they are shown a horizontal arrow pointing either to the left or to the right respectively but to suppress ("stop") their action if they hear an auditory signal (beep) which is presented at varying time intervals just after the visual stimulus. The time interval between visual and auditory signal at which the subjects successfully suppress their action on 50% of the trials ("stop signal reaction time", SSRT) is recorded.

Statistical analysis

Statistical analyses were carried out with SPSS version 22.0. The normality of the distribution of all variables was evaluated with the Shapiro-Wilk test. As most of the investigated variables were not normally distributed, medians and interquartile ranges were used in descriptives, and nonparametric tests were employed in comparisons between groups. Statistical significance was set at 0.05.

Comparison between patients and controls on neuropsychological measures was performed with Mann Whitney test. For the neurocognitive variables with a significant difference among patients and controls Spearman correlation analyses were performed with several clinical characteristics and HPA axis variables. Multiple linear regression analyses using a stepwise procedure were then performed with the specific neuropsychological measures as dependent variables.

The predictors considered were: duration of illness, number of depressive and manic episodes, history of psychotic symptoms, psychopathological state (depressed, elevated or remitted), basal cortisol, delta cortisol, and DST non-suppression as well as current use of antipsychotic and mood stabilizer medication.

All neurocognitive measures, with the exception of SOC that was normally distributed, were subjected to transformations as appropriate (PAL: square root transformation, IED: natural logarithm transformation and SST: inverse transformation).

Results

Subjects

Sixty Bipolar I patients and 30 healthy controls were included in the study. Patients and healthy controls did not statistically differ for age, education and gender distribution (table 1). The clinical characteristics and HPA axis indices of the subjects are shown in table 2. All patients were medicated with the vast majority receiving more than one psychotropic drug. At the time of testing 85% of the subjects were on antipsy-

chotics, 90% on mood stabilizers (16% lithium, 54% valproate) and 45% on antidepressants.

Comparison between patients and controls on neurocognitive functioning

Patients showed significantly poorer performance in visuo-spatial associative learning (PAL), attentional set shifting (IED), planning (SOC) and inhibitory control (SST) than healthy controls, whereas their performance was similar to the control group at the spatial recognition memory task (SRM) (table 1).

Association of clinical variables with neurocognitive functioning

Longer duration of illness was associated with worse performance in PAL ($\rho = -0.328$, $p < 0.05$). Number of manic episodes showed a negative correlation with

Table 1. Comparison of demographic variables and neurocognitive performance between patients and controls

	Bipolar Patients	Healthy Controls	p
	(N=60)	(N=30)	
	Median (interquartile range)		
Demographic factors			
Gender (Men/Women)	23/37	10/20	n.s.
Age	44.5	44.5	n.s.
	(36.00–53.75)	(37.00–54.50)	
Education (years)	12	12	n.s.
Neurocognitive functioning			
Visuo-spatial memory			
SRM %	72.50	75.00	n.s.
	(60.00–80.00)	(63.75–91.25)	
PAL adj err	11.00	4.25	p=0.021
	(4.25–25.75)	(3.00–11.00)	
Executive functions			
SOC tot	6	8	p<0.001
	(5.00–7.00)	(6.75–9.00)	
IED adj err	23.50	16.50	p=0.047
	(14.00–45.25)	(9.00–26.50)	
Inhibitory control			
SST SSRT	216.13	185.48	p=0.021
	(195.00–305.34)	(149.30–234.50)	

SRM %, Spatial Recognition Memory percent correct; PAL adj err, Paired Associate Learning total errors adjusted; IED adj err, Intradimensional/Extradimensional Attentional Set Shifting total errors adjusted; SOC tot, Stockings of Cambridge total problems solved in minimum moves; SST SSRT, Stop Signal Test Stop Signal Reaction Time n.s., non significant

Table 2. Clinical characteristics and Biological parameters of bipolar patients.

Clinical characteristics	Median (IQR)	N (%)
Illness duration	16 (7.25–21.00)	
Age of onset	28 (20.25–35.75)	
HAMD-17 total score	11.5 (4.00–17.75)	
YMRS total score	6 (3.00–15.00)	
GAF score	45 (35–55)	
N. previous depressive episodes	4 (2–6)	
N. previous manic episodes	2 (1–4)	
N. admissions	2 (1–4)	
History of suicide attempts		31 (51.7%)
History of psychotic symptoms		35 (58.3%)
Biological Parameters		
Basal cortisol (µg/dl)	14 (10.75–17.70)	
Δ-cortisol (µg/dl)	10.93 (13.41–7.46)	
DST non-suppression		43 (71.7%)

Most variables showed skewed distributions therefore median and interquartile range (IQR) are given.

HAMD: Hamilton Depression Rating Scale, YMRS: Young Mania Rating Scale, GAF: Global Assessment of functioning, Δ cortisol: difference between basic and post-dexamethasone cortisol, DST: dexamethasone suppression test

IED ($\rho = -0.378$ και $p < 0.01$) and number of depressive episodes was associated with longer reaction time in SST ($\rho = -0.354$ και $p < 0.01$). Lastly, history of psychotic symptoms, current symptomatology and global functioning did not correlate with any cognitive task in our study (table 3).

Association of HPA axis variables with neurocognitive functioning

We examined the relation between neurocognitive performance and HPA axis functioning. Higher levels of basal cortisol were associated with worse performance in visuo-spatial associative learning (PAL) ($\rho = 0.271$, $p < 0.05$), planning (SOC) ($\rho = -0.300$, $p < 0.05$) and SST ($\rho = 0.276$, $p < 0.05$). No statistically significant correlation was found between Δ-cortisol or DST non-suppression and neurocognitive functioning (table 4).

Multiple regression analysis

As shown in Table 5 multiple regression analysis confirmed the correlation of poor performance in PAL with longer illness duration and higher basal cortisol and showed a protective effect of mood stabilizers.

Number of previous manic episodes emerged as the only predictive factor for IED performance. Regarding SOC and SST besides gender and education no other clinical or HPA axis-related factor was correlated.

Discussion

The results of our study confirm and add to the rich literature on the neuropsychological deficits in BD in remission.^{1,2,20,21} Bipolar patients showed poorer performance in neurocognitive tasks than healthy controls matched for age, gender and education. Specifically, they committed more errors in visuo-spatial paired associative memory and learning (PAL) and attentional set shifting (IED) tasks, displayed worse planning ability (SOC) and needed increased time intervals to suppress a prepotent response at the inhibitory control task (SST). On the contrary, in the simpler memory paradigm of spatial memory (SRM) the difference between the two groups was not statistically significant.

This is one of the first studies to address the role of HPA axis on cognition in BD. We found that neurocognitive functioning was associated with basal cortisol as well

Table 3. Non-parametric correlations (Spearman's rho) between clinical variables and neurocognitive performance.

	Visual memory	Inhibitory control	
	PAL adj err	SOC tot	ID/ED adj err
Age	0.200	-0.095	0.234
Gender	0.259	-0.248	0.297*
Education	-0.298*	-0.293*	-0.279*
Illness duration	0.328*	-0.033	0.166
N. depressive episodes	0.080	0.144	-0.003
N. manic episodes	0.098	-0.188	0.378**
HAMD total score	0.109	-0.103	-0.129
YMRS total score	0.024	-0.099	0.201
GAF score	-0.017	0.232	-0.088
History of psychotic symptoms	0.117	0.133	0.044

Figures in bold letters indicate statistical significance; * $p < 0.05$; ** $p < 0.01$

Other abbreviations as in table 1 and 2.

Gender (0=Women, 1=Men)

Table 4. Non-parametric correlations (Spearman's rho) between HPA axis variables and neurocognitive performance.

	Visual memory	Executive functions	
	PAL adj err	SOC tot	ID/ED adj err
Basal cortisol ($\mu\text{g/dl}$)	0.271*	-0.300*	-0.033
Δ -cortisol ($\mu\text{g/dl}$)	-0.014	-0.159	0.008
DST non-suppression	-0.257	-0.137	-0.002

Figures in bold letters indicate statistical significance; * $p < 0.05$; ** $p < 0.01$

Other abbreviations as in table 1 and 2.

as with various indices of illness severity and chronicity such as duration and number of manic episodes. Lastly, regarding the effect of medication, we found that current treatment with mood stabilizers may have a beneficial effect, especially on visuo-spatial associative learning.

Association of clinical variables with neurocognitive functioning

Many studies have reported a negative relationship between duration of illness and visuo-spatial and verbal memory.^{12,22–25} However, the effect of illness duration on paired associative learning has been less explored so far.^{12,26} We found that duration of illness negatively affected performance in PAL, indicating deterioration of visuo-spatial associative memory and learning over time in BD. A mechanism postulated to explain such findings is that, over time, there is an ongoing destructive process that affects primarily

the hippocampus, probably related to the hypercortisolemia that accompanies the occurrence of each episode of depression or mania.³

In line with other studies showing a negative association between number of previous manic episodes and neurocognitive functioning^{22,24,27} we found that number of previous episodes had a significant negative effect on attentional set shifting (IED), implying an increased tendency among patients to perseveration when called to make attentional switches.

We expected to find a negative correlation between mood symptomatology and neurocognitive functioning.^{2,21} However, we observed only not statistically significant weak correlations of manic or depressive symptomatology probably because of the relatively mild affective symptoms in our patients (median HAMD-17 total score 11.5; median YMRS total score 6.0).

Presence of psychotic symptoms was not associated with neurocognitive performance. Negative effects of psychotic symptoms on cognition are described in the literature²⁸ but also absence of any effect.²⁹ A recent meta-analysis on this subject concluded that there is only a modest effect of history of psychosis on the severity of cognitive deficits in BD and that findings do not support a categorical distinction between psychotic and non-psychotic BD.³⁰

Association of HPA axis variables with neurocognitive functioning

Higher basal cortisol levels significantly correlated with worse performance in visual associative memory (PAL), planning (SOC) and inhibitory control (SST) in our study, although the last two correlations were not confirmed in the regression analysis. There are no previous studies examining the relation between visual associative memory tasks and cortisol-related variables in BD, although such tasks are putative indices of the temporo-hippocampal memory system, which is known to be negatively affected by chronic exposure to high levels of glucocorticoids,^{31–34} leading to the postulation that, in bipolar disorder hypercortisolemia, in the long-term, may result in toxicity to the hippocampus, decreased glucocorticoid receptor numbers and ultimately cell death and tissue loss in temporal lobe region.^{3,35}

Similarly to our findings, studies on cognitive function measures other than visuospatial associative memory have shown that a correlation exists between neurocognition and HPA axis activity in mood disorders, although some negative results have also been reported. Thompson et al (2005)¹² observed a significant correlation between executive function and basal salivary cortisol in 63 euthymic bipolar patients; Watson et al (2006)¹³ studied 17 euthymic bipolar patients and reported a significant correlation between patients' post-dexamethasone cortisol and impairment in working memory. Moreover, in unipolar depressed patients, Egeland et al (2005)⁹ found a negative association between high morning cortisol levels and both executive functioning and post-encoding memory. Conversely, a recent study observed no association between various indices of HPA axis activity and neuropsychological measures in a sample of 65 currently depressed or euthymic bipolar patients.¹⁴ It is worth mentioning, however, that researchers used a pattern recognition memory paradigm of visu-

al memory which is a simpler task than the paired associate learning one in our study, which is representative of the kind of learning undertaken in everyday life.

Interestingly, the effect of basal cortisol on visuospatial associative memory in our study seemed to be distinct from psychopathology (symptom severity was not related to cortisol levels; data not shown). This might explain why we have not found any association between neurocognitive measures and delta cortisol or DST suppression, which are often related to current affective state. Our finding is in line with other recent studies in depressed unipolar and bipolar patients that have provided evidence that cortisol levels are dissociated from depression severity in their impact on cognitive function.^{9,14,36,37}

Association of medication and neurocognitive functioning

The effect of medication on cognitive functioning in BD is considered one of the most important confounding factors in literature because it is a very complex issue, difficult to control for.³⁸ Patients are typically assessed while they are receiving a combination of psychotropic drugs like mood stabilizers, antipsychotics and antidepressants. Drugs exert their action on cognitive function at various levels some of which are mediated by their true therapeutic action (i.e. return to euthymia, prevention of new episodes), some are related to their side effects and others to their direct effect on cerebral areas important for cognitive functioning (i.e. neurotrophic action of lithium and valproate in the hippocampus). We found that current treatment with mood stabilizers was associated with better performance in visuo-spatial associative memory. This finding is in line with preclinical studies showing a neuroprotective effect of lithium and valproate in the hippocampus.³⁹ Moreover, a significant increase in grey matter volume was reported after administration of lithium in bipolar patients.⁴⁰ Unfortunately, most evidence to date regarding the effect of antipsychotics and mood stabilizers comes from studies on other clinical populations (patients with schizophrenia and epilepsy) whereas data on BD is limited and controversial.^{41,42} As for the impact of antipsychotic treatment on bipolar patients' neuropsychological function there is evidence pointing to worsening of cognitive performance probably related to antipsychotic-induced psychomotor retardation

which contrasts research findings showing cognitive improvement in schizophrenic patients.^{38,43,44}

Limitations

Part of our bipolar sample did not fulfill stringent criteria for euthymia. Moreover, the associations reported in our study can be interpreted as indicating a progressive disease process leading to a deterioration of cognitive function. It is worth noting that the direction of causality cannot be determined. An unknown underlying factor might cause both illness progression and cognitive dysfunction. Alternatively, there might be a self-reinforcing process in which patients with a more severe course of illness develop cognitive impairment while at the same time patients with cognitive impairment may be more prone to suffer from a more severe and frequently recurring form of disease.

Conclusions

We recorded significant deficits in visual associative learning, attentional set shifting, planning and response inhibition in bipolar patients with respect to healthy controls replicating previous literature findings. However, this was one of the first studies to assess HPA axis function and provide evidence on the relation of basal cortisol with cognitive functioning and especially visual paired associative learning in BD. Moreover, we presented new data on the negative impact of duration of illness and number of previous manic episodes on neurocognitive performance. Lastly, regarding the effect of medication, we detected a beneficial effect of mood stabilizers on visual paired associative learning that warrants further investigation given its clinical relevance.

Παράμετροι λειτουργίας του άξονα υποθαλάμος-υπόφυση-επινεφρίδια (ΥΥΕ) και νευροψυχολογική εκτίμηση σε ασθενείς με διπολική διαταραχή

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Η διπολική συναισθηματική διαταραχή συνδέεται σε πολλές περιπτώσεις με ελλείμματα στις γνωσιακές λειτουργίες αλλά η αιτιολογία αυτών των ελλειμμάτων παραμένει σε μεγάλο βαθμό άγνωστη. Η παρούσα μελέτη εστίασε στην αξιολόγηση της επίδοσης διπολικών ασθενών σε διάφορες νευροψυχολογικές δοκιμασίες στο πλαίσιο του μοντέλου υπερδραστηριότητας του άξονα Υποθάλαμος-Υπόφυση-Επινεφρίδια (ΥΥΕ) καθώς και στις πιθανές συσχετίσεις της νευροψυχολογικής λειτουργικότητας με διάφορα κλινικά χαρακτηριστικά. Στη μελέτη συμμετείχαν 60 ασθενείς με κύρια διάγνωση διπολική διαταραχή (ΔΔ) τύπου Ι καθώς και 30 υγιείς μάρτυρες. Όλοι οι συμμετέχοντες υπεβλήθησαν σε μια σειρά από δοκιμασίες από τη νευροψυχολογική συστοιχία CANTAB προκειμένου να εκτιμηθεί η επίδοσή τους στη μνήμη, στις εκτελεστικές λειτουργίες και στον ανασταλτικό έλεγχο. Η τρέχουσα ψυχοπαθολογία αξιολογήθηκε μέσω των κλιμάκων Hamilton Depression Rating Scale (HAMD) και Young Mania Rating Scale (YMRS) για την κατάθλιψη και τη μα-

νία αντίστοιχα ενώ η εκτίμηση της συνολικής λειτουργικότητας πραγματοποιήθηκε με την κλίμακα Global Assessment of Functioning (GAF). Τέλος, σε όλους τους ασθενείς μετρήθηκαν τα βασικά επίπεδα κορτιζόλης καθώς και τα επίπεδα κορτιζόλης μετά από τη δοκιμασία καταστολής με χορήγηση δεξαμεθαζόνης. Βρέθηκαν στατιστικά σημαντικές διαφορές ανάμεσα σε ασθενείς και σε υγιείς μάρτυρες όσον αφορά στην οπτικο-χωρική συνειρμική μάθηση/μνήμη, την ικανότητα σχεδιασμού και γνωσιακής ευελιξίας καθώς και στον ανασταλτικό έλεγχο. Επιπρόσθετα, παρατηρήθηκε στατιστικά σημαντική αρνητική συσχέτιση ανάμεσα στα επίπεδα βασικής κορτιζόλης και την επίδοση στη δοκιμασία οπτικο-χωρικής συνειρμικής μάθησης/μνήμης. Αντίθετα, τα επίπεδα κορτιζόλης μετά από χορήγηση δεξαμεθαζόνης δεν σχετίστηκαν με τη νευροψυχολογική λειτουργικότητα. Η διάρκεια νόσου παρουσίασε αρνητική συσχέτιση με την επίδοση στην οπτικο-χωρική συνειρμική μάθηση/μνήμη. Επίσης, ο αριθμός προηγούμενων μανιακών επεισοδίων βρέθηκε να σχετίζεται με μειωμένη ικανότητα γνωσιακής ευελιξίας. Η βαθμολογία στις ψυχομετρικές κλίμακες για την κατάθλιψη και τη μανία και η παρουσία ψυχωτικών συμπτωμάτων στο ιστορικό δεν συσχετίστηκαν με την επίδοση στις νευροψυχολογικές δοκιμασίες που εξετάστηκαν. Τα αποτελέσματα της παρούσας μελέτης υποστηρίζουν την ύπαρξη γνωσιακών ελλειμμάτων στη ΔΔ και παρέχουν δεδομένα για τη σχέση των επιπέδων βασικής κορτιζόλης με τη νευροψυχολογική λειτουργικότητα και συγκεκριμένα με την επίδοση στην οπτικο-χωρική μάθηση/μνήμη. Επιπροσθέτως, επιβεβαιώνεται ότι δείκτες βαρύτητας και χρονιότητας όπως η διάρκεια της νόσου και ο αριθμός των προηγούμενων μανιακών επεισοδίων συσχετίζονται με χειρότερες επιδόσεις στις νευροψυχολογικές δοκιμασίες. Είναι γνωστό ότι τα γνωσιακά ελλείμματα στη ΔΔ αφορούν μεγάλο αριθμό ασθενών και επηρεάζουν δυσμενώς την ψυχοκοινωνική και επαγγελματική τους λειτουργικότητα. Ο ρόλος του άξονα ΥΥΕ χρειάζεται να μελετηθεί περαιτέρω ως προς την ανάπτυξη νευροψυχολογικής δυσλειτουργίας στη ΔΔ. Η αναγνώριση ωστόσο παραγόντων που σχετίζονται με τη γνωσιακή λειτουργικότητα, όπως τα βασικά επίπεδα κορτιζόλης και ο αριθμός μανιακών επεισοδίων, δύναται να συνεισφέρει στην ανάπτυξη κατάλληλων προληπτικών και θεραπευτικών παρεμβάσεων.

Λέξεις ευρετηρίου: Διπολική διαταραχή, Άξονας Υποθάλαμος-Υπόφυση-Επινεφρίδια, κορτιζόλη, νευροψυχολογική λειτουργικότητα, οπτική μνήμη, εκτελεστικές λειτουργίες.

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