

Cognitive control in patients with alcohol use disorder: testing a three-function model

Anna V. Trusova, Svetlana G. Klimanova, Anna A. Berezina,
Anton N. Gvozdetskiy

Summary

Background: Cognitive control deficits are believed to contribute to continued alcohol consumption in patients with alcohol use disorder (AUD). The majority of studies exploring cognitive functioning in AUD focused on isolated components of cognitive control. The aim of the current study is to test cognitive control models for explaining cognitive dysfunctions in patients with AUD.

Materials and methods: In total, 53 participants with AUD undergoing detoxification inpatient treatment were assessed using the Brief Assessment of Cognition in Affective Disorders (BAC-A), the Continuous Performance Test, identical pairs (CPT-IP) and the Stroop test.

Results: A model of patients' cognitive control dysfunction is developed using principal component analysis. It includes response inhibition and working memory components and explains 87.3% of cognitive control variance. The comparison between "low" and "high" cognitive control groups yielded significant differences in verbal and working memory ($p < 0.001$), processing speed ($p = 0.006$) and emotional processing ($p < 0.01$) tasks. When compared with the normative data, the low cognitive control group exhibited deficits in working memory, motor skills, processing speed, planning and decision-making, and emotional processing (all at the $p < 0.001$ level). No other significant differences were observed.

Discussion: The cognitive control model, which includes working memory and response inhibition, might be more accurate in explaining cognitive deficits in AUD. The clinically and demographically equal groups differed in cognitive control abilities, motor skills, processing speed and emotional interference control.

Conclusions: This is one of the first studies examining cognitive control in Russian patients with AUD. The findings suggest differences in premorbid cognitive functioning or differences in vulnerability to neurotoxic effects of alcohol among patients with AUD with varying levels of cognitive control.

alcohol dependence, cognitive control, cognitive impairment in AUD.

INTRODUCTION

Multiple studies observed associations between alcohol use disorder (AUD) and impairments in cognitive functioning, more specifically in the areas of object recognition, visuospatial skills, psychomotor speed, learning and memory, and executive functions [1-4]. However, the findings

Anna V. Trusova^{1,2}, Svetlana G. Klimanova², Anna A. Berezina¹, Anton N. Gvozdetskiy¹: ¹Department of Psychology, Division of Medical Psychology and Psychophysiology, Saint-Petersburg State University, Saint-Petersburg, Russia; ²V.M. Bekhterev National Research Medical Center for Psychiatry and Neurology, Saint-Petersburg, Russia

Correspondence address: anna.v.trusova@gmail.com

are not consistent [4,5]. Studies of cognitive control in patients with AUD explain this discrepancy by suggesting that cognitive control deficits have impact on both the onset of AUD and its consequences [5,6].

A meta-analysis conducted by Wilcox et al. [7] has revealed consistent results regarding response inhibition deficits in AUD, while less consistent findings were observed for working memory and distractor interference control. Similar findings were reported in a subsequent study: alcohol consumption had a direct impact on response inhibition and working memory [5]. However, contradictory results were obtained in other studies. For instance, working memory impairments were not observed in patients with advanced stages of alcohol dependence [8]. In another study, while response inhibition deficits were present in patients during a detoxification period, a direct effect of alcohol intake on response inhibition was not observed [9]. Thus it is important to gain understanding of why such inconsistencies occur.

One of the possible explanations is an ambiguous definition of the term cognitive control [10]. Braver and Barch [11] define cognitive control as the internal representation, maintenance and updating of context information in the service of exerting over thoughts and behavior. However, this definition of cognitive control is similar to the concept of executive function. In fact, some authors [7] consider cognitive control to be a subset of executive function. At the same time, Lezak et al. [12] define executive function as individual capacities that allow a person to successfully engage in independent, purposive, self-directed and self-serving behavior. Thus, both the term "cognitive control" and the term "executive function" emphasize the task of engaging in purposive behavior. We suggest that these terms describe two dissimilar approaches to regulative functions. The notion of "executive function" reflects an integrative view, which encompasses complex functions, such as planning, decision-making etc. A major weakness of studies that adhere to this approach includes the task-impurity problem (e.g. not only executive functions are involved in task performance), which leads to low reliability of executive tasks [13,14]. The notion of "cognitive control" is a more fundamental and homogenous approach, as it fo-

cuses on strictly measured functions associated with specific brain regions [15,16]. This suggestion is similar to the componential and emergent approaches to understanding cognitive control described by Cooper [17], although its relation with executive functions has not been fully explained. The author also points out the advantages of a componential view.

The second possible explanation for the inconsistencies in cognitive control studies is linked to the diversity of cognitive control theories and, as a result, diversity in their assessment methods [18]. One of the most prominent theories is the Three Function Theory proposed by Miyake et al. [14], which suggests that cognitive control consists of an inhibition of a prepotent response, mental set-shifting, and information updating and monitoring [14]. These components were extracted from simple and complex executive tasks data using confirmatory factor analysis. Response inhibition is defined as the "ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary" [14, p. 57]. Information monitoring and updating includes maintenance of task-relevant information and the ability to dynamically manipulate the contents of working memory. Mental set-shifting includes "disengagement of an irrelevant task set and the subsequent active engagement of a relevant task set" [14, p. 55]. According to Miyake et al. [14], these three functions have either no linear relationship or very weak intercorrelations, which reflects their independence. The Three Function Theory approach has been used in many AUD studies, but all three functions were not tested simultaneously [5,7]. The most widely studied cognitive control components include response inhibition, distractor interference and working memory. However, these studies had no common theoretical base. Riderinkoff et al. [19] define distractor interference as the individual's ability to resolve response conflict and to deliver a response conflicting with their natural or prepotent response. We suggest that these components can be unified in an empirically based model of cognitive control in AUD.

Thus, one of the possible solutions to the problem of inconsistent results in cognitive control studies is to compare different approaches to cognitive control in a clinical sample. The aim

of this study is to assess cognitive control in patients with AUD according to (1) the Three Function Theory and (2) an empirically based model.

MATERIALS AND METHODS

Participants

Fifty-three participants with alcohol dependence disorder undergoing inpatient detoxification treatment were recruited at the Department of Addictions at V.M. Bekhterev National Research Medical Center for Psychiatry and

Neurology (Saint Petersburg, Russia). All participants had a diagnosis of alcohol dependence according to the International Classification of Diseases (ICD-10). Inpatients who had a history of or current comorbid psychiatric disorder and/or any other significant health conditions preventing them from participation (e.g. severe tremor, weakness) were excluded. The study was approved by the Human Investigation Committee of Saint-Petersburg State University; all participants signed an informed consent form. Participants' demographic data and characteristics of alcohol dependence are presented in Table 1.

Table 1. Demographic and clinical characteristics of the patient sample (n=53)

	Value
Age, years: mean (SD)	41.13 (9.4)
Males: n (%)	39 (73.6)
Education, high school: n (%)	34 (64.2)
Family history of alcohol dependence: n (%)	14 (26.4)
History of traumatic brain injury: n (%)	23 (43.4)
Prior detoxification treatment: n (%)	23 (43.4)
Duration of AUD, years: median (IQR)	10.00 (5.0, 18.0)
Number of remissions from AUD in the past: median (IQR)	1.00 (0.0, 2.0)
Average duration of remissions from AUD in the past, months: median (IQR)	3.00 (0.0, 6.0)
Maximum duration of AUD in the past, months: median (IQR)	6.00 (0.0, 12.0)
HADS anxiety: median (IQR)	8.00 (6.0, 11.0)
HADS depression: median (IQR)	6.00 (3.0, 8.5)
ADS total score: median (IQR)	18.00 (14.0, 22.0)

ADS, AUD, alcohol use disorder; HADS, Hospital Anxiety and Depression Score.

Procedure

All participants were recruited at the end of their inpatient detoxification treatment (i.e. during the second week of hospitalization) prior to discharge. The assessment procedure consisted of two parts and took approximately 3 hours. The first part includes a clinical interview, which focuses on gathering background information and clinical characteristics of the patient's addiction, and completion of self-report measures. The second part involves a cog-

nitve assessment. Both components of the assessment were administered by trained psychologists.

Measures

The cognitive tests included the Russian version of the Brief Assessment of Cognition in Affective Disorders (BAC-A) [20,21], the Continuous Performance Test, identical pairs version (CPT-IP) [22], and the Stroop task [23].

The BAC-A comprises eight tasks evaluating visuomotor abilities (token motor task), working memory (digit sequencing), learning and declarative memory (list learning), attention or processing speed (symbol coding), verbal fluency (category instances (animals) and Controlled Oral Word Association Test (COW-AT) ("B" and "C"-words)), problem-solving (the Tower of London test), affective interference (an affective interference test that includes learning a list of emotional and neutral words and recognition in 20 min), and affective inhibition (emotional Stroop test). Monitoring and updating of working memory (Updating/Working memory) was evaluated with a digit sequencing test. Mental set-shifting (Shifting) was assessed using a verbal fluency task; the shifting parameter is calculated as the difference between semantic fluency test (right answers) and the mean of two trials on the COW-AT (right answers).

The CPT-IP was used to assess inhibition of prepotent responses (Inhibition) [22]. The test was developed by using PEBL, a free software [24]. The task includes series of two-, three – and four-digit sequences. The digits are shown on the screen for 50 ms followed by 950 ms dark time. Participants are instructed to press the space bar when two identical numbers are shown consecutively. The response inhibition index was calculated as a mean of d-prime values (from Signal Detection Theory) for each session.

We modified the Stroop task [23] to enable its comparison with the Russian version of BAC-A affective inhibition task. Participants were presented with sheets of paper containing 4 columns of color names printed in different ink colors (red, blue, green). They were instructed to name the color of the ink (Color naming) of the printed words. Participants were given 30 s to read as many words as they could on each

page. The goal of this task was to determine response interference control (Interference).

Statistical methods

The mean and the median were calculated for demographic data, clinical characteristics and self-report measures. A correlation analysis (Spearman's rho criteria) was conducted to identify relationships between the components of cognitive control. Principal components' analysis was used to determine which components better explain cognitive control functioning in AUD. The groups' cognitive and clinical characteristics were compared using the General Linear Model: Linear and Logistic. Student's t-tests and the Wilcoxon test were used for identifying statistically significant differences between groups as one-sample criteria. The Benjamini–Yekutieli correction was used to reduce the impact of multiple comparisons. Statistical analysis was carried out with the R statistical package [25].

RESULTS

Comparison of cognitive measures with a normative value

A comparison of patients' cognitive characteristics with normative data is presented in Table 2. The normative value is operationalized as 40 T-scores, obtained using a one-sided test. Significant differences were observed in the following subtests: Tower of London ($t=-4.20$; $p<0.001$), token motor task ($t=-4.60$; $p<0.001$), emotional Stroop – color ($t=-2.13$; $p=0.038$), emotional Stroop – neutral color ($V=235.00$; $p<0.001$), emotional Stroop – emotional color ($t=-3.42$; $p=0.001$), affective interference/delayed affective ($V=29.00$; $p<0.001$), and affective interference/cued recall affective ($t=-3.10$; $p<0.001$).

Table 2. Performance on cognitive tests

Subtests	Value: mean (SD)	t/W	p
Verbal memory	44.95 (13.85)	2.60	1.000
Digit sequencing	37.65 (12.36)	-1.38	0.173
Token motor task	31.14 (14.03)	-4.60	<0.001
Verbal fluency	46.80 (10.49)	4.72	1.000
Symbol coding	36.84 (12.18)	-1.89	0.065
Tower of London	28.44 (20.02)	-4.20	<0.001
Emotional Stroop test			
Neutral words	36.59 (12.82)	-1.94	0.058
Color	36.10 (13.33)	-2.13	0.038
Neutral color	32.19 (12.89)	235.00 ^a	<0.001
Emotional color	33.58 (13.68)	-3.42	0.001
Affective interference test:			
Affective sum 3 trials	43.11 (10.69)	2.12	1.000
Non-affective sum 3 trials	44.42 (12.22)	2.63	1.000
Cued recall affective	33.75 (11.38)	-3.10	<0.001
Cued recall non-affective	45.77 (11.89)	3.53	1.000
Delayed affective	26.73 (21.55)	290.00 ^a	<0.001
Delayed non-affective	37.54 (15.89)	656.00 ^a	0.601
Cognitive control functions (subtests used)			
Interference (Stroop task)	29.25 (11.31)		
Working memory (digit sequencing)	16.53 (4.00)		
Shifting (verbal fluency)	9.83 (4.43)		
Inhibition (CPT-IP, d-prime)	1.99 (0.70)		

Superscript "a" indicates V-Wilcoxon criteria; otherwise – Student's t.

CPT-IP, Continuous Performance Test, identical pairs.

TESTING COGNITIVE CONTROL MODELS IN PATIENTS WITH AUD

The Three Function Theory and an empirically based model of cognitive control were tested. The Three Function Theory consists of updating/working memory, inhibition of prepotent response and task-shifting; means of these components are presented in Table 2. The performance on the updating/working memory task was significantly correlated with the inhibition task ($r=0.71$; $p<0.001$). No other significant correlations were observed between cognitive control components. The principal components analy-

sis has shown that the Three Function Model explains 59.7% of variance.

The empirically based model includes working memory, response inhibition and distractor interference controls. These components were chosen in accordance with a meta-analysis carried out by Wilcox et al. [7]. The principal components analysis has shown that this model explains 68.8% of variance. Due to low and comparable values of principal components calculated for both models, an additional model including Inhibition and Working memory was tested. For this model the principal components value is the highest and explains 87.3% of variance. Subsequently, participants were divided into two

groups in accordance with the level of the principal component (i.e. “high” and “low” cognitive control levels). There were no significant differences between these groups in their demographic

or clinical characteristics. However, the low cognitive control group scored significantly higher on the measures of depressive symptoms. More detailed results are presented in Table 3.

Table 3. Demographic and clinical characteristics of “high” and “low” cognitive control groups

Parameter	High cognitive control group	Low cognitive control group	F/ χ^2	p
Total n	23	30		
Age, years: mean (SD)	40.4 (9.5)	41.7 (9.4)	0.08 ^a	0.778
Male: n (%)	15 (65.2)	24 (80.0)	1.43	0.231
Age at onset: mean (SD)	27.7 (9.0)	30.1 (7.9)	1.14 ^a	0.290
High school diploma: n (%)	16 (69.3)	18 (60.8)	0.52	0.473
Family history of alcohol dependence: n (%)	3 (13.0)	11 (36.7)	3.46	0.063
History of traumatic brain injury: n (%)	12 (52.2)	11 (36.7)	1.26	0.261
Prior detoxification treatment: n (%)	12 (52.2)	11 (36.7)	1.98	0.160
Duration of AUD: median (IQR)	10.0 (6.0, 19.0)	8.0 (5.0, 17.8)	0.63	0.427
Number of remission from AUD in the past: median (IQR)	1.0 (0.5, 1.0)	1.0 (0.0, 2.0)	0.35	0.551
Average duration of remissions from AUD in the past, months: median (IQR)	6.0 (1.0, 9.0)	1.0 (0.0, 6.0)	2.90	0.089
Maximum duration of AUD in the past, months: median (IQR)	6.0 (2.0, 13.5)	3.5 (0.0, 11.3)	1.50	0.221
HADS anxiety: median (IQR)	8.0 (6.0, 11.0)	9.0 (7.3, 11.8)	0.66	0.417
HADS depression: median (IQR)	4.0 (2.0, 6.0)	6.0 (4.3, 9.0)	4.12	0.043*
ADS total score: median (IQR)	18.0 (14.0, 25.0)	18.5 (14.0, 21.0)	0.31	0.580

Superscript “a” indicates the linear regression model (F), otherwise – logistic regression model (χ^2).

ADS, AUD, alcohol use disorder; HADS, Hospital Anxiety and Depression Score.

Figure 1 depicts comparisons of cognitive characteristics between high and low control groups. As compared to high cognitive control group, the low cognitive control group had significantly lower results on the following subtests: verbal memory ($\chi^2=10.71$; $p<0.001$), digit sequencing ($F=63.01$; $p<0.001$), verbal fluency ($F=12.53$; $p=0.001$), symbol coding ($F=2.81$; $p=0.006$), emotional Stroop test – neutral word ($F=9.03$; $p=0.004$), emotional Stroop test – color ($F=6.51$; $p=0.014$), emotional Stroop test – neutral color ($F=23.99$; $p<0.001$), emotional Stroop test – emotional color ($\chi^2=12.99$; $p<0.001$), affective interference/affective sum of 3 trials ($F=10.13$; $p=0.002$), affective interference/non-affective sum of 3 trials ($F=15.99$; $p<0.001$), and

affective interference/cued affective ($F=12.76$; $p<0.001$). In comparison with the normative data, the low cognitive control group scored significantly lower in the following subtests: digit sequencing ($t=6.69$; $p<0.001$), token motor task ($t=-5.01$; $p<0.001$), symbol coding ($t=-3.64$; $p=0.006$), Tower of London ($t=-5.14$; $p<0.001$), emotional Stroop test – neutral word ($t=-4.04$; $p=0.002$), emotional Stroop test – color ($t=-3.36$; $p=0.012$), emotional Stroop test – neutral color ($V=7.00$; $p<0.001$), emotional Stroop test – emotional color ($t=-5.18$; $p<0.001$), affective interference/cued affective ($t=-6.05$; $p<0.001$), and affective interference/delayed affective ($t=-4.62$; $p<0.001$). A comparison of the high cognitive

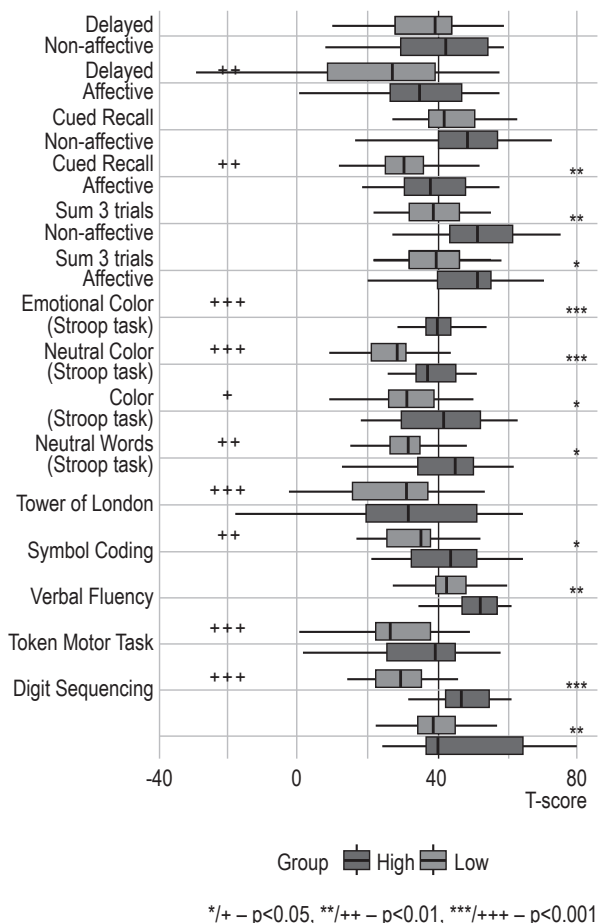


Figure 1. Intergroup differences in cognitive functioning

control group with the normative data did not yield any significant differences.

DISCUSSION

This is one the first studies examining cognitive control in Russian patients with AUD. It was aimed at developing an accurate cognitive control model for explaining the diversity of data on cognitive deficits in patients with AUD. The study also replicates cognitive control and cognitive dysfunction studies in patients with AUD.

The observed cognitive deficits in AUD include impairments in planning and decision-making, motor skills and affective interference control, which is to a certain extent consistent with the results of earlier studies [2,3,26]. With regard to cognitive control abilities in patients

with AUD, the observed deficiencies in working memory and response inhibition are consistent with previous findings, but the present study also observed task-switching or response interference control deficits [5,7]. Neither the Three Function Theory nor the empirically based model fully explain the reported impairments in cognitive control, whereas the dual model, which includes working memory and response inhibition, might be more accurate.

In order to understand the usefulness of the Three Function Theory model, we divided the participants into two groups according to their cognitive control level. Intergroup differences were observed for verbal and working memory, motor skills, processing speed, and the ability to respond to emotional stimuli. A comparison between the low cognitive control group and the normative data yielded deficits in the same functions as well as in planning and decision-making. The obtained data are consistent with other studies [1-4]. The high cognitive control group does not significantly differ from the normative data, which partially corroborates the results obtained by Wollenweber et al. [8] in a group of patients with severe alcohol dependence. The data might reflect a mild degree of cognitive impairment. The fact that clinically and demographically uniform groups have differences in cognitive functioning including cognitive control might indicate differences in pre-morbid cognitive functioning or the diversity in patients' vulnerability to neurotoxic effects of alcohol.

LIMITATIONS

The first limitation of the study is the absence of longitudinal data, which might explain the possible causes for intergroup differences in cognitive functioning. The second limitation is the prevalence of verbal tasks and the lack of visual-spatial measures. The absence of normative data for the CPT-IP and the Stroop task is the third limitation of the study.

Funding

This research was supported by the Russian Foundation for Basic Research (RFBR, Department of Humanities and Social Science) project no. 16-06-01043.

REFERENCES

1. Fitzpatrick LE, Crowe SF. Cognitive and emotional deficits in chronic alcoholics: A role for the cerebellum? *Cerebellum*. 2013;12(4): 520–533.
2. Takahashi TT, Vendruscolo LF, Takahashi RN. Binge-like ingestion of a combination of an energy drink and alcohol leads to cognitive deficits and motivational changes. *Pharmacol Biochem Behav*. 2015; 136: 82–86.
3. Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin Exp Res*. 2000; 24(5): 611–621.
4. Stavro K, Pelletier J, Potvin S. Widespread and sustained cognitive deficits in alcoholism: A meta-analysis. *Addict Biol*. 2012; 18: 203–213.
5. Day AM, Kahler CW, Ahern DC, Clark US. Executive functioning in alcohol use studies: A brief review of findings and challenges in assessment. *Curr Drug Abuse Rev*. 2015; 8(1): 26–40.
6. Dalley JW, Everitt BJ, Robbins TW. Review and top-down cognitive control. *Neuron*. 2011; 69(4): 680–694.
7. Wilcox CE, Dekonenko CJ, Mayer AR, Bogenschutz MP, Turner JA. Cognitive control in alcohol use disorder: Deficits and clinical relevance. *Rev Neurosci*. 2014; 25(1): 1–24.
8. Wollenweber FA, Halfter S, Bru E, Weinberg C, Cieslik EC, Mu VI, et al. Subtle cognitive deficits in severe alcohol addicts – Do they show a specific profile? *J Neuropsychol*. 2014; 8: 147–153.
9. Dry MJ, Burns NR, Nettelbeck T, Farquharson AL, White JM. Dose-related effects of alcohol on cognitive functioning. *PLoS One*. 2012; 7(11): 1–8.
10. Morton JB, Ezekiel F, Wilk HA. Cognitive control: Easy to identify but hard to define. *Top Cogn Sci*. 2011; 3(2): 212–216.
11. Braver TS, Barch DM. A theory of cognitive control, aging cognition, and neuromodulation. *Neurosci Biobehav Rev*. 2002; 26(7): 809–817.
12. Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological Assessment*, 5th ed. New York: Oxford University Press; 2012.
13. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci USA*. 2006; 103(52): 19878–19883.
14. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howarter A, Wager TD. The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cogn Psychol*. 2000; 41(1): 49–100.
15. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001; 24: 167–202.
16. Botvinick MM, Cohen JD. The computational and neural basis of cognitive control: Charted territory and new frontiers. *Cogn Sci*. 2014; 38(6): 1249–1285.
17. Cooper RP. Cognitive control: Componential or emergent? *Top Cogn Sci*. 2010; 2(4): 598–613.
18. Trusova AV, Klimanova SG. Kognitivnyj kontrol pri alkoholnoj zavisimosti obzor sovremennyh issledovanij [in Russian]. *Klin i Med Psihol Issled obuchenie Prakt ehlektronnyj nauchnyj zhurnal*. 2015; 3. Available from: http://medpsy.ru/climp/2015_3_9/article12.php
19. Wiers RW, Gladwin TE, Hofmann W, Salemink E, Ridderinkhof KR. Cognitive bias modification and cognitive control training in addiction and related psychopathology: Mechanisms, clinical perspectives, and ways forward. *Clin Psychol Sci*. 2013; 1(2): 192–212.
20. Yanushko MG, Shamanina MV, Aristova TA, Keefe RS, Ivanov MV. Standartizaciya shkaly: Kratkaya ocenka kognitivnyh funkcij u pacientov s affektivnymi rasstrojstvami (BAC-A) na osnove normativnyh dannyh rossijskoj populyacii [in Russian]. *Ross Psihiatr zhurnal*. 2015; 2: 68–75.
21. Keefe RSE, Fox KH, Davis VG, Kennel C, Walker TM, Burdick KE, et al. The Brief Assessment of Cognition in Affective Disorders (BAC-A): Performance of patients with bipolar depression and healthy controls. *J Affect Disord*. 2014; 166: 86–92.
22. Cornblatt BA, Lenzenweger MF, Erlenmeyer-Kimling L. The Continuous Performance Test, Identical Pairs Version II: Contrasting attentional profiles in schizophrenic and depressed patients. *Psychiatry Res*. 1989; 29(1): 65–85.
23. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935; 18: 643–662.
24. Mueller ST, Piper BJ. The Psychology Experiment Building Language (PEBL) and PEBL Test Battery. *J Neurosci Methods*. 2014; 222: 250–259.
25. Team RC. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2017.
26. Fitzpatrick LE, Jackson M, Crowe SF. The relationship between alcoholic cerebellar degeneration and cognitive and emotional functioning. *Neurosci Biobehav Rev*. 2008; 32(3): 466–485.