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Relationships of Behavioral Measures of Frontal Lobe Dysfunction with Underlying Electrophysiology in Cocaine-Dependent Patients

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Abstract

Background and Objectives—Despite evidence that frontal lobe functioning is impaired in cocaine-dependent individuals, relationships between behavioral measures of frontal dysfunction and electrophysiological measures of inhibition in cocaine use have not been explored.

Methods—Using the Frontal System Behavior Scale (FrSBe), frontal dysfunction was assessed in a group of abstinent cocaine-dependent subjects (N=49) and healthy controls (N=32). Using transcranial magnetic stimulation (TMS) and evoked potential (EP)-based electrophysiological measures of inhibition, we assessed associations between these measures and FrSBe estimates of frontal dysfunction.

Results—Patients had significantly higher FrSBe scores for executive dysfunction, disinhibition and apathy than controls. Lower TMS-based resting motor thresholds (i.e., hyperexcitability) were significantly associated with higher Executive Dysfunction scores in the patients.

Conclusions and Scientific Significance—Relationships between FrSBe scores and TMS-based measures highlight neurophysiological aberrations underlying frontal lobe dysfunction in cocaine abusers. TMS and EP measures may be useful probes of the intermediary steps between frontal lobe dysfunction and addictive behavior.

1. Background and Objectives

Functional neuroimaging and neuropsychological studies suggest that chronic cocaine use can alter anterior brain structure and function. Relative to healthy controls, cocaine dependent subjects exhibit reduced cerebral blood flow and brain glucose metabolism,^{1–2} primarily in frontal cortex. They also exhibit impaired frontal executive cognitive functions and correspondingly lower frontal gray matter tissue density that does not normalize with six

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

weeks of abstinence,³⁻⁴ as well as reduced inferior frontal white matter integrity that is associated with higher cognitive impulsivity.⁵

The Frontal Systems Behavior Scale (FrSBe), formerly known as the frontal lobe personality scale,⁶ provides brief and valid measures of three frontal system-related behavioral domains: Apathy, Disinhibition, and Executive Dysfunction.⁷ Damage to the dorsolateral prefrontal cortex is linked to FrSBe executive dysfunction; damage to mesial frontal and anterior cingulate cortex is linked to apathy and akinesia; and damage to orbitofrontal cortex is linked to disinhibition and emotional outbursts.⁸ Although individuals with frontal lobe damage may perform within normal limits on neuropsychological tests,⁹ their social and occupational functioning in natural settings can be severely impaired.¹⁰ The FrSBe could fill a gap in the assessment of frontal system integrity by providing a way to quantify these behavioral problems so they may be targeted for treatment. However, minimal data are currently available on the ecological validity of the FrSBe. To date, several studies have shown that cocaine abuse is associated with frontal lobe behavioral problems across different FrSBe domains.¹¹⁻¹⁵ The present study aimed to replicate and extend those findings using electrophysiological measures.

Sensory gating reflects cerebral cortical ability to inhibit incoming excess sensory input and is typically measured using evoked potential (EP) paradigms.¹⁶ Specifically, two identical auditory stimuli (S1 & S2) are delivered with a short inter-stimulus interval (ISI). Sensory gating has been conceptualized as a complex multi-stage function including P50, N100 and P200 phases of information processing.¹⁶ Its capacity is operationally defined as the ratio of the amplitude of the second to the first responses (S2/S1) and should reflect at a larger degree the inhibition of redundant input (S2) rather than a differential response to S1 stimuli.¹⁷ Acute cocaine administration exerts a deleterious effect on sensory gating in rats.¹⁸ Repeated cocaine administration disrupted sensory gating in rats for at least nine days after cessation of cocaine exposure.¹⁹ These findings have been replicated.²⁰⁻²¹

Non-invasive transcranial magnetic stimulation (TMS) is also a promising tool for examining cortical inhibitory functions. TMS is measured using three main parameters. First, TMS motor threshold (MT) is defined as the intensity of the magnetic pulse needed to induce a motor EP or muscle contraction when stimulating the motor cortical area. The MT is hypothesized to reflect sodium channel conductivity and neuronal membrane stability.²² Second, cortical silent period (CSP) is defined as the duration of interruption of ongoing voluntary muscle contraction (refractory interval of suppressed EMG signal) induced by TMS of the motor cortex and represents a cortical inhibitory phenomenon. Third, paired-pulse inhibition is defined as the extent to which an initial stimulus suppresses a response to a second stimulus (procedurally similar to EP sensory gating described above), which specifically reflects GABA-dependent inter-neuronal inhibitory processes.²³

Sensory gating and TMS measures of cerebral inhibitory processes differ significantly in abstinent cocaine-dependent versus healthy control subjects,²⁴⁻²⁹ indirectly inferring to impaired function of frontal lobes.³⁰ While EP-based sensory gating studies have uniformly found decreased inhibition in cocaine-dependent versus control subjects,²⁰ TMS studies of cocaine-dependent patients have produced mixed results including both increased

inhibition,^{24,26} and increased excitability.^{28–29} No previous studies have attempted to examine EP and TMS measures concurrently in the same cocaine-dependent individuals. These multimodal measures may have different underlying neural mechanisms; therefore, examining them in the same individuals could be informative.

To evaluate frontal lobe dysfunction associated with chronic cocaine use and the underlying pathophysiology, we hypothesized that (1) behavioral measures obtained by FrSBe would reflect significant frontal lobe problems in abstinent cocaine-dependent patients (i.e., increased Apathy, Executive Dysfunction and Disinhibition) versus healthy controls; and (2) these increased FrSBe scores in cocaine abusers would be associated with reduced inhibitory function reflected in TMS and EP-based electrophysiological measures.

2. Methods

2.1. Subjects and clinical screening

The study was approved by the Wayne State University Human Investigation Committee and the University of Wisconsin-Madison Social and Behavioral Sciences Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Inclusion criteria for cocaine-dependent subjects—(1) Males and females between ages 18–55; (2) Subjects meeting DSM-IV criteria for cocaine-dependence, ascertained using the substance abuse section of the SCID interview; (3) drug and alcohol abstinence for at least three weeks (verified via current treatment provider), but not longer than one year since last use. All cocaine-dependent subjects were recruited from treatment and/or long-term rehabilitation programs. These programs routinely employ urine drug screens at least twice weekly and verified the duration of abstinence self-reported by the subjects. *Inclusion criteria for healthy controls*: (1) Males and females between ages 18–55, matched for age and gender to subjects in the cocaine-dependent group; (2) No lifetime history of psychiatric illness.

Exclusion criteria for both cocaine-dependent and control groups—(1) Serious medical illness (e.g., major cardiovascular, neurological, renal, or endocrine disorders); (2) Past or present psychiatric illness unrelated to cocaine use; (3) Current or lifetime diagnosis of physiological dependence on alcohol or other drugs (except cocaine for patients' group, and nicotine or caffeine for both groups). Use or abuse of alcohol or marijuana strictly within the context of ameliorating the stimulating effects of cocaine was allowed as long as criteria for dependence on these substances were not fulfilled. Experimentation with heroin or phencyclidine was allowed if it did not exceed five occasional (total lifetime) uses and the last occurrence was at least five years prior to testing; (4) Pregnancy as assessed by urinalysis prior to each TMS procedure if not done within the previous two weeks; (5) Positive urine toxicology screen the day of the study; (6) Current or recent use (within 6-weeks) of over-the-counter or prescription psychoactive drugs (antidepressants, anxiolytics, antipsychotics, mood stabilizers, and psychostimulants); (7) While no formal cognitive testing was performed, subjects must be judged to be cognitively intact by bed side examination. Subjects had to be able to read, fully understand and retain details of the different parts of the study. Subjects with any difficulty in this task were excluded. (8) Exclusions from the

TMS procedures were: a) History of seizures (including drug related seizures) or any other neurological problem; and b) magnetizable metal objects in the head.

The same sequence of tasks was used in all subjects after screening procedures: FrSBe, EP followed by TMS tasks.

2.2. The Frontal Systems Behavior Scale (FrSBe)

The Frontal Systems Behavior Scale (FrSBe)⁷ was used to measure behaviors associated with changes or damage to frontal systems. Participants were instructed to rate the extent to which the behavioral description applied to them 'at present' on a 5-point scale (from 1 [almost/never] to 5 [almost always]). Higher FrSBe scores indicate relatively more abnormal behavior and implied frontal system dysfunction.⁸ The 46-item behavioral rating scale yields a total score as well as scores on three subscales: Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items). Coefficient α is high for the overall measure for both the patient (0.92) and the control (0.90) groups. In the patient group, Cronbach's α was observed to be adequate on all three FrSBE subscales: Apathy (.83), Disinhibition (.74), and Executive Dysfunction (.82). For the controls, the internal consistency of the FrSBE subscales was fair to adequate: Apathy (.78), Disinhibition (.76), and Executive Dysfunction (.72).

FrSBe analysis—Raw FrSBe scores were used in all the analyses examining associations with electrophysiological measures. For purposes of clinical interpretation, the raw FrSBe scores were converted into T-scores using the T-score tables provided in the FrSBe manual, taking into account participants' age, gender, and educational level⁷. A T-score of 65 is considered the cutoff for indicating clinically significant neurobehavioral abnormalities, whereas T-scores in the 60–64 range are indicative of borderline dysfunction. Participant groups' average T-scores for each of the subscales as well as the total scale, and the proportion of participants scoring in the associated ranges of functional levels (namely, normal functioning, borderline impaired, and clinically significant impairment) were noted.

2.3. Evoked potentials and sensory-gating measurements

Data acquisition—EEG data were recorded and processed from 19 sites of the International 10/20 Electrode Placement System using a linked-ears reference and 0.3–100Hz analog bandpass filter settings (Amplifier Model-12C; Grass Inc., Quincy, Massachusetts). Preprocessing of EEG data included digital filtering (1–50 Hz), segmentation (–0.1 to 0.4 s), baseline correction (using prestimulus interval), artifact rejection and averaging to obtain auditory EPs of interest (P50, N100, P200). A paired-click paradigm was administered (STIM presentation software, Neuroscan). The sensory gating paradigm involved presentation of two identical auditory stimuli, S1 and S2 (duration=4ms, rise/fall=1ms, intensity=85dB, frequency=1000 Hz). Inter-stimulus and inter-pair intervals were set to vary randomly between 500 ± 25 ms and 8 ± 1 s, respectively. Subjects were instructed to relax, stay awake and fixate a point on the wall. Amplitudes of the P50, N100 and P200 responses to both S1 and S2 stimuli and gating ratios ($S2/S1 \times 100$) were scored using data from the Cz electrode site. P50/N100/P200 were scored as the largest peaks during the intervals 35–80, 70–150, and 150–300 ms from S1 and S2 onset, respectively.

Peak-to-peak amplitudes were measured between the peak and preceding trough (for P50 and P200) or preceding positivity (for N100). Gating ratios were calculated from peak-to-peak amplitudes for S1 and S2 ($S2/S1 \times 100$ in %). Lower gating ratios reflect stronger gating, and vice versa.

2.4. TMS measures

We assessed the following measures using both left and right hemisphere stimulation: (1) Resting motor threshold as percentage of maximum machine output; (2) Active motor threshold (AMT as % maximum machine output); (3) Cortical silent period (CSP, in ms) at 6 different intensities: 100, 110, 120, 130, 140 and 150% of AMT; (4) Short interval cortical inhibition (SICI) and facilitation (ICF), expressed in percentage as ratios [test stimulus amplitude / single stimulus amplitude] at ISI = 3 and 10 ms, respectively; (5) Long interval cortical facilitation and inhibition (LICF and LICI, respectively) expressed in percentage as ratios [test stimulus amplitude / single stimulus amplitude] at ISI of 30, 50, 100 and 150 ms; and (6) Stimulus intensity curves (SIC) at 6 intensities: 100, 110, 120, 130, 140 and 150% of RMT, and 50, 60, 70, 80, 90 and 100% of maximum machine output. For detailed description of TMS measures and procedures, see Gjini et al.²⁹

2.5. Statistical analyses

Relationships among FrSBe subscale scores were first assessed by computing Pearson's correlation coefficients. Multivariate analysis of variance (MANOVA), with FrSBe subscale score as a dependent measure (Apathy, Disinhibition, Executive Dysfunction) and Group (patient, healthy) as between-subjects variable, was used to compare the FrSBe subscale scores. Upon significant differences, post-hoc two-tailed independent samples Bonferroni-corrected *t*-tests were used to compare the two groups in terms of frontal function based upon the FrSBe subscale scores. Associations between electrophysiological measures of inhibition (EP-based sensory gating and TMS-based motor cortical excitability) and behavioral measures of frontal function from FrSBe were evaluated using multiple regression analyses by entering the three FrSBe subscores in the first step, as well as adding in duration of cocaine abstinence and former cocaine-use variables in the second step as predictors in separate regressions for each EP and TMS measure. Finally, associations between duration of cocaine abstinence, prior history of cocaine use, and behavioral measures of frontal function from the FrSBe were evaluated by computing Pearson's correlation coefficients, upon nonsignificant results from a normality check based on the Kolmogorov-Smirnov test.

3. Results

3.1. Participant Characteristics

Forty-nine abstinent cocaine-dependent patients (45 men and 4 women, mean $\pm$ SD age 42.6 $\pm$ 8.0 years) and thirty-two healthy controls (27 men and 5 women, age 41.7 $\pm$ 9.4 years) completed this study. Both samples consisted of predominantly African-American male subjects (4 and 2 Caucasian subjects, as well as 4 and 5 female subjects among patients and controls, respectively). Prior to their treatment episode, the patients had a history of regular cocaine use of 15.9 $\pm$ 7.4 years with average consumption of 4.8 $\pm$ 3.4 grams per week.

Abstinence duration was 4.6 ± 3.4 months. The value for the Kolmogorov-Smirnov statistic on abstinence duration data was nonsignificant ($p=0.086$), consistent with a normal distribution.

The patients had a significantly larger proportion of cigarette smokers than the healthy controls, $\chi^2(1) = 25.51$, $p < 0.001$, though not in terms of coffee consumption ($\chi^2(1) = 1.55$, $p = 0.21$). Due to possible effects of nicotine and caffeine on cortical excitability, subjects were not allowed to smoke or drink any caffeine-containing product beginning a few hours prior to both EP and TMS sessions. Only 4 healthy subjects were smokers and 1 of them had a score of 7 from Fagerstrom tolerance scale (7–11 would reflect physical dependence on nicotine). In addition, 34 abstinent-cocaine subjects were smokers, two who scored 7 and two who scored 8.

3.2. Associations between self-report measures of frontal functioning

The three FrSBe measures of frontal lobe-based behavioral impairment were significantly correlated with one another in both abstinent cocaine-dependent patients and healthy controls (Apathy–Disinhibition: [patients] $r = 0.70$, $p < 0.001$; [controls] $r = 0.65$, $p < 0.001$; Apathy–Executive Dysfunction: [patients] $r = 0.81$, $p < 0.001$; [controls] $r = 0.85$, $p < 0.001$; Disinhibition–Executive Dysfunction: [patients] $r = 0.76$, $p < 0.001$; [controls] $r = 0.68$, $p < 0.001$).

3.3. Group comparisons of frontal lobe functioning

MANOVA showed a statistically significant difference in FrSBe subscale scores between the two groups, $F(3,77) = 9.01$, $p < .0001$; Wilk's $\Lambda = 0.74$, partial $\eta^2 = 0.26$. Two-tailed Bonferroni-corrected t-tests indicated that compared to healthy controls, the patients scored significantly higher on Apathy (31.29 ± 9.69 vs. 25.22 ± 7.18 ; $t_{77} = 3.23$, $p < 0.01$), Disinhibition (32.67 ± 8.2 vs. 25.19 ± 6.7 ; $t_{79} = 4.30$, $p < 0.001$), and Executive Dysfunction (40.55 ± 10.33 vs. 30.34 ± 7.67 ; $t_{79} = 4.79$, $p < 0.001$). These results are provided in Figure 1.

Table 1 provides the average FrSBe T-scores for the healthy control and the patient groups. It also provides the proportion of participants in each group whose scores fell into the clinically significant range of impairment for each of the FrSBe subscales and for the total scale. About half (24 of 49, or 49.0%) of the patient group produced total FrsBe scores that were in the clinically significant range of impairment. In contrast, only 25% (8 of 32) of the healthy controls had total scores that fell in the clinically significant range.

3.4. Associations of self-report measures of frontal-cortical dysfunction with electrophysiology in the patients' group

Multiple regression analysis showed a significant inverse association between the FrSBe Executive Dysfunction score and the right side RMT measure ($r^2 = 0.146$; $\beta = -0.84$, $t = -2.51$, $p = 0.016$), i.e. higher executive dysfunction was associated with a lower resting motor threshold which reflects increased cortical excitability (Figure 2). Addition of duration of cocaine abstinence and former cocaine-use variables in the regression model did not significantly change this association. A linear regression model with right side RMT as

the dependent variable and executive dysfunction score, group and executive dysfunction score X group interaction as independent variables, showed a significant difference in slopes of the fitted regression lines between the two groups (coefficient for the interaction: $\beta = -1.64$, $p = 0.045$).

A significant association was observed between the FrSBe Disinhibition score and the right side CSP measure at an intensity of 130%-of-AMT ($r^2 = 0.273$; $\beta = 0.55$, $t = 2.54$, $p = 0.015$), i.e. higher disinhibition was associated with longer cortical silent period (Figure 3A).

The FrSBe Disinhibition subscore was also significantly associated with the left side SIC measure at an intensity of 130%-of-RMT ($r^2 = 0.25$; $\beta = -0.44$, $t = -1.79$, $p = 0.05$), i.e. higher disinhibition was associated with weaker responses to single pulse stimulation (Figure 3B). Addition of duration of cocaine abstinence and former cocaine-use variables in the regression model did not significantly change the latter two associations. A linear regression model with SIC measure as the dependent variable and disinhibition score, group and disinhibition score X group interaction as independent variables showed a significant difference in slopes of the fitted regression lines between the two groups (coefficient for the interaction: $\beta = -1.68$, $p = 0.03$). Finally, another linear regression model with the CSP measure as the dependent variable and disinhibition score, group and disinhibition score X group interaction as independent variables showed no significant difference in slopes of the fitted regression lines between the two groups (coefficient for the interaction: $\beta = -1.51$, $p = 0.13$).

After excluding 4 and 1 subjects with mild nicotine dependence from patient and control groups, respectively, results remained significant. No significant associations were observed between EP-measures of response amplitudes and sensory gating with FrSBe behavioral data. We found no significant associations between length of recent abstinence and former cocaine use duration and scores from the FrSBe subscales.

4. Discussion and Conclusions

In this study, abstinent cocaine-dependent patients demonstrated significant frontocortical-related behavioral impairment on FrSBe Disinhibition, Executive Dysfunction and Apathy dimensions. This profile is consistent with an existing but limited literature showing a generalized pattern of abnormal scores in substance dependent individuals across the three FrSBe domains.¹² To our knowledge, this is the first study to probe frontal functions of a carefully selected and relatively large sample of abstinent cocaine-dependent patients, relative to a matched group of healthy controls. Significant group differences were marked on all three behavioral subscales.

The estimates of behavioral dysfunction obtained from the self-reported FrSBe scores are consistent with frontal abnormalities reported in neuroimaging studies. Recent fMRI studies have shown abnormal activation in the anterior cingulate and orbitofrontal cortex regions when processing drug-related cues in cocaine addiction.³¹ Structural abnormalities have also been revealed in the orbitofrontal cortex of cocaine users, such as decreased gray matter in ventromedial orbitofrontal, anterior cingulate and anteroventral insular cortex.³⁻⁴

In the present sample of abstinent cocaine-dependent patients, higher Executive Dysfunction was significantly related to lower TMS-based resting motor thresholds, i.e. greater cortical excitability. This association is directionally opposite of that in healthy controls (i.e., lower Executive Dysfunction was significantly related to lower TMS-based resting motor thresholds). This group divergence could be driven by significantly higher resting motor thresholds in patients versus controls (reflecting decreased neuronal membrane excitability),²⁹ which may constitute an adaptive change to increased cortical excitability mediated by excitatory neurotransmitters, such as glutamate.

In addition, higher Disinhibition was paradoxically associated with weaker responses to single pulse stimulation and to stronger cortical inhibitory function from the CSP-130% TMS measure. A plausible explanation for the latter could involve mediation of CSP through GABA-B receptor neurotransmission, but a different mechanism driving disinhibition in these patients. For example, another TMS measure of cortical excitability (ICF-10ms), thought to be mediated mainly by glutamatergic neurotransmission, showed a trend association with higher Disinhibition scores. These relationships show that the observed dysbalance in cortical excitation/inhibition in cocaine-dependent patients,²⁹ mediated by different neurotransmitter systems (i.e., glutamate, GABA), is reflected in significant deficits in frontal lobe function as probed by FrSBe measures.

Recent findings suggest that frontal system dysfunction is present before stimulant-abuse onset and worsens with repeated stimulant use.¹⁵ Recent controlled clinical studies have also highlighted some promising medications for treating cocaine dependence, especially agents that influence glutamatergic (e.g., N-Acetylcysteine) and GABAergic (vigabatrin) function.³² Thus, evidence suggests that both glutamate and GABA, the brain's primary excitatory and inhibitory neurotransmitters, respectively, modulate the pharmacological effects of cocaine and the resolution of these effects during prolonged abstinence. This suggests that the TMS measures used here could be useful for evaluating the effects of such medications on frontal lobe-related behavioral function, and their effects on recovery of function.

One limitation of the current study is that it relied on self-report of present function rather than obtaining self- and informant-reports for present and past states. The cross-sectional design made it impossible to compare these cocaine-dependent individuals' FrSBe scores during their former period of cocaine abuse versus current state of abstinence. We were unable to obtain data regarding patients' pre-treatment episodes of cocaine abstinence/relapse, nor post-treatment relapse. A longitudinal study could address these issues as well as enable examination whether frontal lobe dysfunction may reflect the sequelae, a comorbid process, or risk factor associated with cocaine use. Another limitation of the present investigation is our failure to include a behavioral assay of frontal lobe functioning such as the Wisconsin Card Sorting Test (WCST)^{33,34} or the Controlled Oral Word Association Test.³⁵ Future studies would be strengthened by the inclusion of such behavioral measures along with the self-report measure.

5. Scientific significance and future directions

Observed relationships in the present study suggest potential neurophysiological mechanisms underlying frontal lobe dysfunction in cocaine-dependent patients. Electrophysiological measures of cortical disinhibition studied here may represent intermediary steps in translating frontal lobe dysfunction to behavioral dysfunction. By repeated assessment of frontal lobe integrity/function, cocaine craving, neurophysiological measures and prospective evaluation of actual relapse behavior, the interrelationships between these variables may be ascertained.

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Figure 1. Mean FrSBe subscale measures of apathy, disinhibition and executive dysfunction in each group. Error bars represent standard error of the mean.

Figure 2.

Association between right side resting motor threshold and FrSBe measure of executive dysfunction in cocaine dependent individuals (partial $r = -0.38$). The linear regression line for control data is also shown for comparison (statistics showed a significant difference in slopes of the fitted regression lines between the two groups).

Figure 3.

A) Association between right side CSP-130% measure from TMS and FrSBe measure of disinhibition in cocaine dependent individuals (partial $r = 0.38$). The linear regression line for control data is also shown for comparison (statistics showed no significant difference in slopes of the fitted regression lines between the two groups).

B) Association between left side SIC-130% measure from TMS and FrSBe measure of disinhibition in cocaine dependent individuals (partial $r = -0.29$). The linear regression line for control data is also shown for comparison (statistics showed a significant difference in slopes of the fitted regression lines between the two groups).

TABLE 1

Comparison of group's T-Scores for Frontal Systems Behavior Scale (FrSBe) and proportion of FrSBe scores that fell within the Clinically Significant Range (operationally defined as T-scores greater than or equal to 65).

FrSBe measures	Group's T-Scores for FrSBe Means ($\pm$ SD)		Proportion of FrSBe Scores That Fell Within the Clinically Significant Range		
	Healthy NonPatient	Patient	Healthy NonPatient	Patient	χ^2
	N=32	N=49	N=32	N=49	
Apathy	50.7 (16.8)	65.9 (23.1)	28.1%	49.0%	3.49
Disinhibition	47.6 (13.9)	63.5 (18.8)	12.5%	38.8%	6.57**
Executive dysfunction	50.1 (15.3)	71.0 (21.2)	15.6%	65.3%	19.26***
Total	49.2 (18.5)	72.1 (25.1)	25.0%	59.2%	9.12**

*
p < 0.05

**
p < 0.01

p < 0.001