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Frontal Systems Deficits in Stimulant-Dependent Patients: Evidence of Pre-illness Dysfunction and Relationship to Treatment Response

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Abstract

BACKGROUND—Frontal systems dysfunction is present in stimulant-dependent patients. However, it is unclear whether this dysfunction is a pre-morbid risk factor or stimulant-induced, is severe enough to be clinically relevant, and if it is relevant to treatment response. These questions were addressed using the Frontal Systems Behavior Scale (FrSBe), a reliable and valid self-report assessment of three neurobehavioral domains associated with frontal systems functioning (Apathy, Disinhibition, and Executive Dysfunction, summed for a Total), that assesses both pre- and post-morbid functioning, and has a specific cutoff for defining clinically significant abnormalities.

METHOD—Six sites evaluating 12-step facilitation for stimulant abusers obtained the FrSBe from 180 methamphetamine- and/or cocaine-dependent participants. Dichotomous treatment response measures included self-reported stimulant use, stimulant urine drug screens, and treatment completion.

RESULTS—A substantial percentage of participants retrospectively reported clinically significant neurobehavioral abnormalities prior to lifetime stimulant abuse initiation (e.g., 67.5%

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Contributors

Drs. Winhusen, Adinoff, and Somoza conceptualized and designed the study. Ms. Kropp and Dr. Horigian provided oversight of data collection. Mr. Lewis and Dr. Winhusen analyzed and interpreted the data. Drs. Winhusen and Adinoff drafted the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Adinoff has served as a consultant for Shook, Hardy & Bacon LLP (medical malpractice consultant, tobacco companies). All other authors declare that they have no conflicts of interest.

on FrSBe-Total) with a significant increase in the proportion reporting such abnormalities for current functioning (86% on FrSBe-Total; p<0.0001). Treatment response was significantly worse for participants with, relative to those without, clinically significant Disinhibition as measured by treatment non-completion (31.6% vs. 15.6%, OR=2.51) and self-reported stimulant use during treatment (40.5% vs. 16.7%, OR=3.40).

CONCLUSION—These findings suggest that frontal systems dysfunction is present prior to stimulant-abuse onset and worsens with stimulant use. Disinhibition may be a prime target for intervention in stimulant-dependent individuals.

Keywords

cocaine; methamphetamine; stimulant; prefrontal cortex dysfunction; FrSBe

1. INTRODUCTION

Frontal systems functioning is necessary for inhibiting inappropriate behaviors, assessing reward salience, flexible mental processing, and complex planning. Many of these functions are impaired in addictive disorders, particularly stimulant dependence (Adinoff et al., 2007; Goldstein and Volkow, 2011; Verdejo-Garcia et al., 2006a). Stimulant-dependent individuals, for example, demonstrate difficulty inhibiting pre-potent responses (Ersche et al., 2012; Fillmore and Rush, 2002), inappropriately assess the relative value of rewards and consequences (Bechara et al., 2001; Verdejo-Garcia et al., 2007), and self-report greater impulsivity (Moeller et al., 2005) relative to healthy controls. Frontal systems dysfunction in stimulant-dependent individuals is substantiated by neuroimaging studies (Garavan, 2011; Goldstein et al., 2011) revealing anatomical or functional alterations in the orbitofrontal (Adinoff et al., 2011; Alia-Klein et al., 2011; Ersche et al., 2005, 2012), dorsolateral (Ersche et al., 2012; Goldstein et al., 2007), medial (Goldstein et al., 2007), and anterior cingulate (Kaufman et al., 2003) cortex circuits.

Despite the relatively rich neurocognitive and imaging literature supporting frontal systems alterations in stimulant-dependence, uncertainties persist. First, the etiology of frontal systems disturbances remains in question. Poor self-control has been shown to predict later substance use and abuse (Moffitt et al., 2011; Wills et al., 2000), but an association between drug use severity and degree of impulsivity suggests a direct toxic effect of the substance on frontal systems (Moeller et al., 2001). Second, the severity of frontal systems dysfunction has been questioned. Many studies have yielded either null or small differences in neurocognitive measures in controls and stimulant-dependent individuals (Jovanovski et al., 2005) and, even when present, it has been questioned whether these differences are severe enough to be clinically meaningful (Hart et al., 2012). Third, the relevance of frontal systems functioning to treatment response remains uncertain. Although some investigators have reported that frontal systems functioning is associated with treatment response (Moeller et al., 2001; Streeter et al., 2008), these studies have relatively small sample sizes and use a variety of measures. Finally, the myriad assortment of neurocognitive tests and self-report questionnaires, as well as varied neuroimaging measures, offer little guidance on the optimal approach to assessing frontal systems functioning in addicted individuals in either clinical or research settings.

The Frontal Systems Behavior Scale (FrSBe) (pronounced ‘fr-zbi') offers an easily administered assessment of three neurobehavioral domains reflective of frontal systems functioning: Apathy, Disinhibition, and Executive Dysfunction (Grace and Malloy, 2001; Malloy and Grace, 2005; Verdejo-Garcia et al., 2006a). The FrSBe has demonstrated reliability (Grace and Malloy, 2001; Stout et al., 2003; Velligan et al., 2002). In addition, the

FrSBe demonstrates construct (Grace et al., 1999; Lane-Brown and Tate, 2009; Paulsen et al., 2000; Velligan et al., 2002; Verdejo-Garcia et al., 2006a), convergent (Norton et al., 2001; Velligan et al., 2002; Verdejo-Garcia et al., 2006a), and ecologic (Boyle et al., 2003; Chio et al., 2010; Reid-Arndt et al., 2007; Rymer et al., 2002) validity. Importantly, the FrSBe has demonstrated discriminant validity [i.e., sensitivity between patients with cortical vs. subcortical disease (Cahn-Weiner et al., 2002; Paulsen et al., 1996) and Frontotemporal Dementia vs. Alzheimer's Disease (Malloy et al., 2007)]. Finally, retrospectively obtained pre-illness scores have been used to demonstrate behavioral changes due to multiple sclerosis (Chiaravalloti and DeLuca, 2003). The FrSBe can be administered as either a self- or informant-assessment, does not require special staff training and has normative data (stratified for gender, age and education; normed with a Caucasian sample) from which to determine T-scores, with a specific cutoff for defining clinically significant neurobehavioral abnormalities (Grace and Malloy, 2001).

Some research has evaluated substance using populations with the FrSBe. In a small study of substance users, Total and subscale FrSBe raw scores (T-scores were not reported) were higher in polysubstance users relative to non-polysubstance users, particularly on the Disinhibition subscale (Spinella, 2003). Several studies, conducted by Verdejo-Garcia and colleagues in Spain, have evaluated poly-substance abusing patients with the FrSBe and have found that substance abusers scored higher than normal controls (Verdejo-Garcia et al., 2006a), that FrSBe scores were related to use severity for some substances (Verdejo-Garcia et al., 2006b), and that cocaine use correlated with Disinhibition (Verdejo-Garcia et al., 2006b). T-scores were not calculated for these studies since they were conducted outside of the U.S., which makes the applicability of the U.S. FrSBe normative data questionable (Verdejo-Garcia and Perez-Garcia, 2008). The import of these past findings is difficult to discern since the clinical significance of FrSBe scores is determined by the ranges established for the FrSBe T-scores. The need to confirm that performance is outside the normal range for a test has recently been raised by Hart et al. (2012) who noted that, while significant differences have been observed between normal controls and methamphetamine-dependent patients on neurocognitive assessments, the scores of the dependent patients typically were within the normal range, and thus, were unlikely to be of clinical significance (Hart et al., 2012).

There has been no published data on the FrSBe in a U.S. sample of stimulant-dependent patients. The FrSBe's clinical and ecological relevance, ease of use, rapid administration, normative data, and ability to retrospectively assess pre-illness and present functioning make it ideal for evaluating questions of functional severity, etiology (pre- vs. post-drug use onset), and relevance to treatment response in stimulant-dependent patients in the U.S. To assess these questions, we administered the FrSBe to a sample of cocaine- and methamphetamine-dependent patients in a multi-site, ancillary study to a National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) trial on 12-step facilitation for stimulant abusers (STAGE-12). STAGE-12 was designed to evaluate the efficacy of a 12-Step facilitation intervention, relative to substance abuse treatment as usual, in improving outcomes in stimulant abusing individuals.

2. METHOD

2.1 Participants

Six participating substance abuse community treatment programs (CTPs), located in Columbus, Ohio, Dallas, Texas, Eugene, Oregon, Jacksonville, Florida, Portland, Oregon, and Seattle, Washington, recruited stimulant abusers participating in the STAGE-12 trial. Participants in the STAGE-12 trial were adults seeking outpatient substance use disorder (SUD) treatment who had used stimulants in the prior 60 days and had a current diagnosis of

stimulant abuse or dependence based on the DSM-IV Checklist (Hudziak et al., 1993). All participants were deemed by a study clinician to be medically and psychiatrically stable enough for participation based on medical history and the Addiction Severity Index-Lite (McLellan et al., 1992) interview. The 180 eligible participants for the present study were randomized into the STAGE-12 trial, endorsed methamphetamine or cocaine as the primary drug of choice, did not have a seizure disorder or a history of stroke, and completed the FrSBe. All participants signed an informed consent form that was approved by the Institutional Review Boards of the participating sites.

2.2 Procedures

See Donovan et al (2011) for a description of the STAGE-12 study procedures. Briefly, methamphetamine- and/or cocaine-abusing participants who met eligibility criteria were randomized to Stimulant Abuser Groups to Engage in 12-Step (STAGE-12) or treatment as usual (TAU). Participants randomized to TAU received treatment as ordinarily provided by the site (minimum of 5–15 hours of treatment weekly). Participants assigned to STAGE-12 received a combination of five group and three individual sessions that replaced the three individual and five group sessions typically provided at the clinic. STAGE-12 is a comprehensive and systematic introduction to 12 Step recovery and fellowship (e.g., literature, meeting attendance, etc.). While it was anticipated that similar activities might be present in TAU, they would likely vary considerably based on the counselor's experience with 12-step and would not follow a systematic approach. Participants in the present study completed a single session in which baseline characteristics and behavioral measures were obtained including the FrSBe. This ancillary testing session was typically completed within a week following randomization into the STAGE-12 trial. More specifically, the average time between randomization and testing was 7.4 days (SD=3.6).

2.3 Measures

The FrSBe is written at a 6th-grade reading level and consists of 46 self-report items, with responses in a five-point Likert-type scale. The FrSBe assesses three domains: Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items); these three domains are summed to yield a total score. The FrSBe instructs the respondent to rate the frequency with which each of the 46 behaviors was engaged in during two time-frames: "Before the illness or injury," referred to as the "Before" rating, and "At the present time," referred to as the "Present" rating. For the current study, participants were instructed that the Before rating referred to the period of time before they started abusing stimulants. While obtaining the informant-based version of the FrSBe would have been ideal, many stimulant-dependent patients are estranged from the family who might serve as informants; thus, the decision was made to utilize only the self-report version of the FrSBe.

Participants in the STAGE-12 trial were scheduled to complete a 5–8 week intervention period. To assess treatment completion, study staff used clinic records to document each participant’s attendance during the first 8 weeks of the STAGE-12 trial, which provided information for each participant’s full intervention period. Completers were defined a priori as those who attended the first 5 weeks of treatment without missing two or more consecutive weeks. The measures of stimulant use included self-report of use for each day of the study assessed using the Timeline Follow-Back procedure (Fals-Stewart et al., 2000) and qualitative urine drug screen (UDS) results. The stimulants screened for by the UDS were cocaine, methamphetamine, and amphetamine. Since approximately half of the sample did not use stimulants during treatment and follow-up, we decided that the question of success or failure in maintaining abstinence was more relevant than actual levels of stimulant use. Therefore the analyses evaluating the relationship between frontal systems dysfunction and stimulant use were based on binary indicators of whether the respective measures (self-

report or UDS) indicated success or failure in maintaining abstinence over the respective periods (treatment phase or follow-up). Research visits were completed at screening/baseline, study weeks 2, 4, and 8, and at three and six months following the randomization. In accordance with National Institutes of Health policy, participants self-reported their race and ethnicity; reporting was based on the race/ethnicity classifications used in the 2000 United States Census. The Patient Health Questionnaire (PHQ; Spitzer et al., 1999) was used to assess for the PHQ diagnoses of Major Depressive Syndrome, other Depressive Syndrome, Panic Syndrome, and other Anxiety Syndrome. Studies have found good agreement between PHQ diagnoses and those of independent mental health professionals (kappa = 0.65; Spitzer et al., 1999).

2.4 Data analysis

All raw FrSBe scores from the Present ratings were converted into T-scores using the T-score tables provided in the FrSBe manual, which are categorized according to age, gender, and educational level (Grace and Malloy, 2001). Because the FrSBe is designed for use in adults only, the Before raw scores were converted to T-scores only for individuals who were at least 18 years of age when they initiated stimulant use (N=118). For all FrSBe scales, T-scores ≥ 65 indicate clinically significant neurobehavioral abnormalities, while T-scores of 60 to 64 indicate borderline dysfunction (Grace and Malloy, 2001). Comparisons of FrSBe scores between methamphetamine-dependent and cocaine-dependent patients revealed no significant differences (data not shown) and thus the groups were pooled for all analyses. The analyses in the present paper did not include covariates, the rationale for which is that the covariates typically considered for inclusion in this type of analysis (e.g., other SUDs, ADHD, mood disorders, etc.) might be related to both stimulant dependence, given the high prevalence rate of other disorders in stimulant-dependent patients, and to frontal systems dysfunction (Robbins et al., 2012) and, thus, might result in controlling for the phenomenon of interest.

The 118 participants with Before and Present FrSBe T-scores were included in the analysis determining the prevalence of clinically significant neurobehavioral abnormalities prior to the initiation of stimulant abuse and evaluating whether significant worsening of neurobehavioral function is associated with use. This analysis determined the percentages of participants reporting clinically significant neurobehavioral abnormalities both before the initiation of stimulant abuse and at present. It then tested for a significant difference in these percentages using the McNemar Exact Test (Q_M). The 180 participants with Present FrSBe T-scores were included in the analysis evaluating whether clinically significant neurobehavioral abnormalities were associated with treatment response. These analyses entailed using Pearson Chi Square tests to compare treatment completion and stimulant use rates for participants with, and without, significant abnormalities as measured by their Present FrSBe T-scores.

3. RESULTS

3.1 Sample Characteristics

Table 1 provides the demographic and clinical characteristics of the 118 stimulant-dependent participants with Before and Present FrSBe T-scores (i.e., those who were at least 18 years old when they initiated stimulant use) and the 180 with Present FrSBe T-scores. The participants were approximately 40 years of age and had 12 years of education on average. Table 2 provides the average FrSBe Present T-scores and proportion of participants scoring in the ranges of normal functioning, borderline impaired, and clinically significant neurobehavioral deficits. The average T-scores for each of the FrSBe scales was above the cut-off for clinically significant neurobehavioral abnormalities (T≥65), suggesting that the

sample as a whole reported significant deficits. A majority of participants scored in the clinically significant range for Apathy (84.2%), Disinhibition (74.7%), Executive Dysfunction (68.2%) and FrSBe Total (81.1%).

3.2 Frontal systems dysfunction prior to stimulant abuse initiation and presently

Table 3 provides the proportion of participants with clinically significant neurobehavioral abnormalities as a function of FrSBe scale and time (i.e., before life-time initiation of stimulant abuse and presently) for the subset of participants (n=118) for whom data from both time points were available. A substantial percentage of patients retrospectively reported clinically significant neurobehavioral abnormalities prior to lifetime stimulant abuse initiation based on the Before FrSBe ratings with a significant increase in the proportion reporting such abnormalities as measured by the Present ratings. For example, on the FrSBe Total scale, the proportion of participants scoring in the significant range was 67.5% for Before ratings and 86% for Present ratings (Q_M=16.3, p<0.0001). These results are consistent with the hypothesis that stimulant abuse is associated with a significant increase in frontal systems dysfunction.

3.3 Relationship between frontal systems dysfunction and treatment response

Table 4 displays the results of the analyses evaluating whether clinically significant neurobehavioral abnormalities were associated with treatment response. While treatment response generally appeared worse for those scoring in the clinically significant range (T≥65) as measured by the Disinhibition, Executive Dysfunction, and Total scales, the difference was only significant for Disinhibition. Specifically, participants with clinically significant Disinhibition were significantly more likely to be treatment non-completers (31.6% vs. 15.6%, OR=2.51) and significantly more likely to report stimulant use during treatment (40.5% vs. 16.7%, OR=3.40), relative to participants with normal or borderline-levels of Disinhibition.

3.4 Supplemental analyses

Approximately 40% of the study sample had a mood disorder, raising the question of whether the high rate of clinically significant neurobehavioral abnormalities observed is due to the prevalence of mood disorders in this sample. To address this issue, the proportion of participants with clinically significant neurobehavioral abnormalities, as measured by the Present FrSBe, were compared between those with (N=69) and without a mood disorder (N=100). The results revealed that those with a mood disorder had a significantly higher proportion of participants with clinically significant Disinhibition (X^2 (2)=15.3, p<0.001) and Total score (X^2 (2)=8.4, p<0.05) but did not differ significantly on Apathy (P=0.0083, p=0.12), or Executive Dysfunction (X^2 (2)=5.1, p=0.08). While the rate of clinically significant neurobehavioral abnormalities was significantly higher in those with a mood disorder relative to those without, the rates were still high in those without a mood disorder (66.3% for Disinhibition and 75.3% for Total). In addition, analyses of the relationship between mood disorder and treatment response (i.e., completion and stimulant use) revealed no significant effects for mood disorder (data not shown).

Approximately 72% of the study sample met criteria for abuse or dependence on a substance other than cocaine or methamphetamine, raising the question of the impact of non-stimulant substance use diagnosis (SUD) on the observed neurobehavioral abnormalities. To address this issue, the proportion of participants with clinically significant neurobehavioral abnormalities, as measured by the Present FrSBe, were compared between those with (N=131) and without a non-stimulant SUD (N=52). The results revealed no statistically significant differences for Apathy (F=0.01, p=0.10), Disinhibition (X^2 (2)=4.0, p=0.13), Executive Dysfunction (X^2 (2)=0.4, p=0.82), or Total (F=0.04, p=0.74).

Approximately 44% of the present sample was Caucasian. As mentioned earlier, the FrSBe was normed with only Caucasians and, thus, the creators of the FrSBE note that it should be interpreted with caution when used with minorities (Grace and Malloy, 2001). To evaluate how sample composition might have impacted our findings, we compared minority participants (N=102) with non-Hispanic Caucasians (N=77) on the proportion of participants with clinically significant neurobehavioral abnormalities, as measured by the Present FrSBe. The results revealed no statistically significant differences for Apathy (X^2 (2)=3.5, p=0.18), Disinhibition (X^2 (2)=2.1, p=0.36), Executive Dysfunction (X^2 (2)=2.4, p=0.30), or Total (X^2 (2)=1.4, p=0.50).

4. DISCUSSION

The present results revealed that stimulant-dependent patients reported clinically significant neurobehavioral abnormalities, as measured by the FrSBe, and that a substantial percentage of participants retrospectively reported such abnormalities prior to lifetime initiation of stimulant abuse. In addition, stimulant abuse appears to be associated with worsening frontal systems dysfunction as demonstrated by the significant increase in participants reporting current clinically significant neurobehavioral abnormalities relative to those reporting pre-existing abnormalities. Clinically significant Disinhibition was associated with worse treatment response as measured by treatment completion and self-reported stimulant use during the treatment phase.

To our knowledge, this is the first evaluation of a sample of U.S. substance-dependent patients using the FrSBe. This is of import in that the present sample could be compared to the FrSBe normative sample, which was a U.S. sample, to determine the clinical significance of the scores. Past research using the FrSBe to evaluate substance using and abusing individuals (Spinella, 2003; Verdejo-Garcia et al., 2006a; Verdejo-Garcia et al., 2006b; Verdejo-Garcia and Perez-Garcia, 2008) has not included a comparison to the FrSBe normative sample, typically due to the study being conducted outside of the U.S., which makes the applicability of the U.S. norms questionable (Verdejo-Garcia and Perez-Garcia, 2008). The finding that a substantial percentage of participants retrospectively reported clinically significant neurobehavioral abnormalities prior to lifetime initiation suggests that frontal systems dysfunction may be a risk factor for becoming stimulant dependent, which is consistent with previous studies demonstrating that self-control during childhood is predictive of substance dependence in adulthood (Caspi et al., 1996; Moffitt et al., 2011). It is also consistent with a recent finding that, relative to normal controls, brain abnormalities in fronto-striatal regions were present in both stimulant-dependent patients and their non-addicted siblings, suggesting that these abnormalities might increase vulnerability for developing stimulant dependence (Ersche et al., 2012). It is also consistent with a recent U.K. study evaluating 22 opioid-dependent and 22-matched control participants on the FrSBe which found that FrSBe abnormalities in the opioid-dependent sample pre-dated substance-abuse initiation based on retrospective report (Pluck et al., 2012).

The proportion of stimulant-dependent patients reporting clinically significant neurobehavioral abnormalities (81.1% on the FrSBe Total) is surprisingly high given that this population typically does not evidence such dramatic neurocognitive deficits (Hart et al., 2012). The prevalence of mood disorders in the present sample does not account for these findings in that, while the rates of clinically significant neurobehavioral abnormalities were higher in those with, compared to without, mood disorders, the rates observed in those without a mood disorder were substantial, suggesting that high rates of neurobehavioral abnormalities are present in the absence of a mood disorder. The FrSBe has demonstrated construct (Grace et al., 1999; Lane-Brown and Tate, 2009; Paulsen et al., 2000; Velligan et al., 2002; Verdejo-Garcia et al., 2006a), convergent (Norton et al., 2001; Velligan et al.,

2002; Verdejo-Garcia et al., 2006a), and discriminant (Cahn-Weiner et al., 2002; Malloy et al., 2007; Paulsen et al., 1996) validity as a measure of maladaptive behavior associated with damage to frontal brain systems. Still, the present sample may differ from the FrSBe normative sample on factors not related to stimulant-dependence but that might be associated with neurobehavioral deficits. If this were the case, then the rates of behavioral deficits observed in stimulant-dependent patients, relative to matched normal controls, may not be as extreme as those observed based on the FrSBe normative data alone. This potential issue should be addressed in future research in which the FrSBe is administered to stimulant-dependent patients and to a matched normal control group.

As noted earlier, individuals with frontal systems dysfunction can evidence neurobehavioral deficits while still performing within normal ranges on neurocognitive tests (Malloy and Grace, 2005). Thus, the high rates of clinically significant neurobehavioral abnormalities observed in the present study might indicate that the FrSBe is a more sensitive test of frontal systems dysfunction relative to neurocognitive tests used in prior stimulant-dependence research. While the rate of clinically significant Apathy was high in this sample (e.g., 84.2% reported significant Apathy), clinically significant Disinhibition (reported by 74.7% of the sample) was the only FrSBe subscale significantly related to treatment response. The finding that clinically significant Disinhibition was associated with treatment response is consistent with past research finding an association between impulsivity and substance abuse treatment response (Moeller et al., 2001; Patkar et al., 2004; Schmitz et al., 2009). This finding, combined with past research, suggests that disinhibition may be an important therapeutic target in stimulant-dependent patients.

The present study has several strengths and limitations. A clear strength of the present study is that it was conducted at multiple sites, which enhances the generalizability of the results, and included a relatively large sample of stimulant-dependent participants. Another study strength is that it was conducted with individuals seeking SUD treatment at CTPs and, thus, the results are likely generalizable to individuals in treatment for stimulant-dependence disorders, which is important when identifying potential therapeutic targets (Winhusen et al., 2012). A limitation of the study was reliance on self-report of functioning rather than obtaining both self- and informant-reports. A study with Spanish poly-substance abusers revealed that FrSBe scores from patient self-report did not differ significantly from informant-report when reporting about periods of abstinence but that self-report, relative to informant-report, of neurobehavioral abnormalities was significantly lower when a period of substance use was rated, suggesting that substance abusers may be less self-aware of their problematic functioning during use periods (Verdejo-Garcia and Perez-Garcia, 2008). Other research has also found evidence of impaired insight in cocaine-dependent patients (Moeller et al., 2010). Future research should thus obtain both self- and informant-reports to assess inter-rater agreement. Another limitation was that the pre-stimulant-abuse-functioning ratings entailed retrospective rating of behavior that occurred many years prior and the reliability of the FrSBe for such retrospective reporting has not been published. Future research should assess the test-retest reliability of such reporting. Another limitation is that the FrSBe is designed for use in adults only and while we eliminated the retrospective ratings for those whose stimulant use started prior to age 18, we did not specifically instruct participants to limit their retrospective ratings to the period of their adulthood. Thus, some of the retrospective ratings might have included ratings of childhood and/or adolescent behavior. In addition, the majority of the present sample was female and limited sample sizes of unimpaired males on the FrSBe subscales prevented analyses of gender effects in the relationship between clinically significant neurobehavioral abnormalities and treatment response. Also, the present study was not powered to evaluate site effects and so the relative importance of site was not evaluated.

Another important limitation of the present study is that it is correlational in nature and, thus, cause and effect determinations cannot be made. In addition, the study was conducted with a stimulant-dependent sample that abused other substances and, thus, the observed associations cannot be attributed solely to stimulant use. Finally, the FrSBe is thought to assess behavior reflective of the functioning of the dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex circuits (Malloy and Grace, 2005; Verdejo-Garcia et al., 2006a). However, the present study did not include imaging and thus the degree to which the FrSBe is associated with frontal systems imaging results in stimulant-dependent patients is unknown; this could be the subject of future research.

The present study revealed that stimulant-dependent patients evidence frontal systems dysfunction as measured by the FrSBe, that frontal systems dysfunction was present prior to the initiation of stimulant abuse based on retrospective ratings, that stimulant use was associated with significant worsening of frontal systems function, and that clinically significant Disinhibition was associated with poorer treatment response. The study results suggest that the FrSBe may have utility in evaluating the role of frontal systems dysfunction in stimulant-dependence. Future research to replicate, and expand on, the present findings seems warranted.

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Table 1

Demographics and clinical characteristics of study samples

	Sample with Pre-Stimulant FrSBe Data (N=118)	Stimulant-Dependent Sample (N=180)
Age (years)	40.6 (8.2)	38.5 (9.3)
Education (years)	12.2 (1.4)	12.0 (1.6)
Male (%)	33.9%	31.7%
Race (%):		
White	35.9%	43.6%
Black	56.4%	46.4%
Other/Mixed	7.7%	10.1%
Ethnicity-Hispanic (%)	4.3%	5.6%
Stimulant Positive UDS[a] (%)	18.6%	20.7%
Stimulant use days in last 30	4.7 (5.8)	4.9 (6.3)
Stimulant Route of Administration:		
Smoking	79.3%	73.0%
Oral / Nasal	11.2%	10.1%
IV	9.5%	16.9%
Age of Onset of Stimulant Use	23.6 (5.5)	20.8 (6.0)
Years of Stimulant Use	12.6 (7.9)	12.1 (7.6)
Years of Non-Stimulant Use	16.6 (11.2)	15.0 (10.5)
Non-Stimulant SUD[b] Diagnosis (%)	72.9%	72.2%
Stimulant-Dependence Diagnosis:		
Methamphetamine	21.4%	25.7%
Cocaine	76.1%	68.7%
Both	2.6%	5.6%
Mood/anxiety disorder	40.9%	40.7%

Note: Where not specifically indicated, numbers represent means (standard deviations).

[a] Urine drug screen

[b] Substance use disorder

Table 2

T-scores and level of functioning for Frontal Systems Behavior Scale (FrSBe) subscales

	T-scores		Level of functioning		
	N	**Mean (SD)**	**Normal (T<60)**	**Borderline (T=60–64)**	**Significant Neurobehavioral Deficits (T≥65)**
Apathy	166	76.9 (12.9)	7.9%	7.9%	84.2%
Disinhibition	167	77.5 (17.5)	14.6%	10.7%	74.7%
Executive Dysfunction	169	73.0 (13.7)	16.8%	15.1%	68.2%
Total	165	79.4 (15.7)	9.1%	9.7%	81.1%

Drug Alcohol Depend. Author manuscript; available in PMC 2014 January 01.

Table 3

Proportion of participants with FrSBe[a]-reported neurobehavioral abnormalities before initiation of stimulant abuse and at present

	N	Clinically Significant Abnormalities Prior to Stimulant Abuse Initiation	Present Clinically Significant Abnormalities	Change in Functioning (Pre-Post Stimulant Abuse Initiation)
Apathy	116	74.1%	87.9%	Q_M[b]=10.7, p=.002
Disinhibition	116	57.8%	77.6%	Q_M[b]=17.1, p<.001
Executive Dysfunction	117	48.7%	74.4%	Q_M[b]=21.4, p<.001
Total	114	67.5%	86.0%	Q_M[b]=16.3, p<.001

[a] Frontal Systems Behavior Scale

[b] McNemar Exact Test Statistic

Table 4

Treatment completion and stimulant use as a function of clinically significant neurobehavioral abnormalities as measured by the FrSBe[a]

		Stimulant Use – Treatment Phase		Stimulant Use – Follow-Up	
	Treatment Non-Completers	**Positive UDS[b]**	**Stimulant Use SR[c]**	**Positive UDS[b]**	**Stimulant Use SR[c]**
Apathy Abnormalities:					
Present (n=149)	27.5%	24.8%	32.9%	43.8%	45.6%
Absent[d] (n=28)	28.6%	24.0%	40.7%	31.8%	40.9%
Analysis Test Statistic (p), Odds Ratio	X^2 (1) = 0.0 (0.91), OR=0.95	X^2 (1) = 0.0 (0.93), OR=1.05	X^2 (1) = 0.6 (0.43), OR=0.71	X^2 (1) = 1.1 (0.29), OR=1.67	X^2 (1) = 0.2 (0.68), OR=1.21
Disinhibition Abnormalities:					
Present (n=133)	31.6%	26.2%	40.5%	45.2%	47.3%
Absent[d] (n=45)	15.6%	20.0%	16.7%	33.3%	36.1%
Analysis Test Statistic (p), Odds Ratio	X^2 (1) = 4.3 * (0.04), OR=2.51	X^2 (1) = 0.6 (0.43), OR=1.42	X^2 (1) = 7.9 ** (0.005), OR=3.40	X^2 (1) = 1.6 (0.21), OR=1.65	X^2 (1) = 1.4 (0.24), OR=1.59
Executive Dysfunction Abnormalities:					
Present (n=122)	30.3%	26.8%	38.3%	43.8%	45.1%
Absent[d] (n=57)	24.6%	17.6%	25.9%	38.3%	46.8%
Analysis Test Statistic (p), Odds Ratio	X^2 (1) = 0.6, (0.43) OR=1.34	X^2 (1) = 1.6 (0.20), OR=1.71	X^2 (1) = 2.5 (0.12), OR=1.77	X^2 (1) = 0.4 (0.52), OR=1.26	X^2 (1) = 0.0 (0.85), OR=0.93
Total Abnormalities:					
Present (n=142)	29.6%	24.6%	37.6%	45.0%	44.4%
Absent[d] (n=33)	18.2%	23.3%	21.9%	25.0%	46.4%
Analysis Test Statistic (p), Odds Ratio	X^2 (1) = 1.7 (0.19), OR=1.89	X^2 (1) = 0.0 (0.88), OR=1.07	X^2 (1) = 2.8 (0.09), OR=2.15	X^2 (1) = 3.7 (0.05), OR=2.45	X^2 (1) = 0.0 (0.85), OR=0.92

[a] Frontal Systems Behavior Scale

[b] Urine drug screen

[c] Self-report

[d] Scored in the range or normal or borderline functioning.

* $p < 0.05$,

** $p < 0.01$