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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% 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.

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

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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 'frɪzbi') 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 et al. (2006a) in Spain, have evaluated poly-substance abusing patients with the FrSBe and have found that substance abusers scored higher than normal controls, 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-drug 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 multisite, 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 h 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