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Executive dysfunction and reward dysregulation: A high-density electrical mapping study in cocaine abusers

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ABSTRACT

Executive function deficits and reward dysregulation, which mainly manifests as anhedonia, are well documented in drug abusers. We investigated specific aspects of executive function (inhibitory control and cognitive control), as well as anhedonia, in a cohort of current cocaine abusers in order to ascertain to what extent these factors are associated with more severe drug dependence. Participants filled out questionnaires relating to anhedonia and their addiction history. Participants also performed a response inhibition task while high-density event-related potentials (ERPs) were recorded. Electrophysiological responses to successful inhibitions (N2/P3 components) and to commission errors (ERN/Pe components) were compared between 23 current users of cocaine and 27 non-using controls. A regression model was performed to determine the association of our measures of reward dysregulation and executive function with addiction severity. As expected, cocaine users performed more poorly than controls on the inhibitory control task and showed significant electrophysiological differences. They were also generally more anhedonic than controls. Higher levels of anhedonia were associated with more severe substance use, whereas the level of executive dysfunction was not associated with more severe substance use. However, N2 amplitude was associated with duration of drug use. Further, inhibitory control and anhedonia were correlated, but only in controls. These data suggest that while executive dysfunction characterizes drug abuse, it is anhedonia, independent of executive dysfunction, that is most strongly associated with more severe use.

1. Introduction

Substance dependence is a multi-faceted problem. Substance abusers not only grapple with the inability to control and inhibit drug seeking behavior, but also with reward dysregulation. Reward dysregulation is usually manifested as anhedonia, the inability to experience pleasure from activities usually found enjoyable. In this study, we sought to gain a better understanding of the relationship between higher-order cognitive control and anhedonia in drug addiction, with a focus on users of cocaine. The study had two goals. The first was to assess the ability of cocaine users to successfully inhibit a prepotent response tendency and to see to what extent deficits in this ability is associated with addiction severity. The second was to examine the role of affective dysregulation in drug abuse and how this affective dysregulation may be associated with inhibitory capabilities in cocaine users.

The ability to withhold inappropriate responses and to monitor one's actions fall under the umbrella of executive function. A well established paradigm to probe inhibition and monitoring is the Go/No-Go response inhibition task, which requires subjects to overcome a prepotent response tendency established by frequent Go stimuli to successfully inhibit response execution to No-Go stimuli. Inhibitory capability is measured by the number of correct withholds to No-Go stimuli, and performance monitoring can be measured by examining reaction time adjustments following incorrect executions to No-Go stimuli. Those who abuse drugs, including cocaine, have consistently demonstrated difficulties in their abilities to inhibit responses (Fillmore et al., 2002; Kaufman et al., 2003; Hester and Garavan, 2004; Garavan and Hester,

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2007; Verdejo-Garcia and Perez-Garcia, 2007; Garavan et al., 2008). Other work has revealed inhibitory difficulties in cocaine addiction that correlate to amount of cocaine used (Albein-Urios et al., 2012). We and others have shown that intact inhibitory processes (Connolly et al., 2012; Bell et al., 2013; Morie et al., 2013) have been observed in those who are in recovery from drug dependence. Comparatively less is known about impairments in performance monitoring in cocaine abuse, though both behavioral and electrophysiological work has indicated deficits (Li et al., 2006; Franken et al., 2007a; Hester et al., 2007). Hester et al. (2007) assessed performance monitoring with post-error adjustments in response time and also the participants' awareness of their errors as indicated by an additional button press. Cocaine using participants showed comparable post error slowing to controls when they were aware of their errors, but demonstrated awareness of fewer of their errors. These findings suggested that it is lack of awareness of errors that drives performance monitoring difficulties in cocaine abusers. Combined, the work in inhibitory control and error monitoring has suggested a strong role for executive dysfunction in cocaine addiction, and a need to determine to what extent inhibitory control and performance-monitoring deficits contribute to addiction severity, or vice versa. Understanding to what degree these specific components of executive functioning are associated with more severe cocaine addiction will enhance the development of more targeted interventions.

It is also important to examine the role of affective dysregulation. It is well established that cocaine's subjective effects arise due to its impact on the re-uptake of the neurotransmitter dopamine. This neurotransmitter plays a strong role in reward and reward motivation (Wise, 2008). Dopamine D2 receptors are down-regulated in response to the high levels of DA that circulate as a result of cocaine use, resulting in poorer dopamine transmission when the drug is not being used (Wyatt et al., 1988; Martinez et al., 2004, 2005, 2007; Volkow et al., 2007; Fehr et al., 2008). This poor transmission contributes to reward dysregulation. In this study, we focused specifically on drug user's inability to derive adequate subjective reward from everyday stimulation. This reduction in reward response is typically referred to as anhedonia. Drug abusers have demonstrated higher levels of anhedonia than controls (Janiri et al., 2005; Franken et al., 2007b; Leventhal et al., 2010), and anhedonia is a key feature of withdrawal from many substances, including cocaine and methamphetamine (Barr et al., 2006; D'Souza and Markou, 2010). The Reward Deficiency Syndrome theory of addiction proposes that reward deficiency associated with anhedonia may contribute to an increased desire for sources of high reward, such as drugs of abuse (Blum et al., 2000).

Both reward dysfunction and executive dysfunction may interact to worsen severity of substance abuse. This relationship has been suggested in gambling addicts, who showed increased self reported impulsivity that was correlated to sensitivity to reward during a gambling task (Alvarez-Moya et al., 2011). Previous work has suggested the presence of a relationship between direct measures of anhedonia and executive capabilities, notably in schizophrenia (Herbener et al., 2005; Tully et al., 2012). It has also been suggested that the presence of anhedonia may worsen executive capabilities as resources are put toward managing the affective dysregulation (Cheetham et al., 2010). Indeed, affective dysregulation in depressed individuals is known to affect performance monitoring capabilities (Holmes and Pizzagalli, 2007, 2008). The current study sought to determine the extent of anhedonia and deficits in inhibitory control and monitoring in healthy controls and in current cocaine abusers.

To study the behavioral and cortical underpinnings of inhibition and performance monitoring, control and cocaine-dependent participants performed a Go/No-Go task while high density event related potentials (ERPs) were recorded. The ERP components associated with successful inhibition are well characterized (Pfefferbaum et al., 1985; Eimer, 1993; Kiefer et al., 1998; Roche et al., 2005; Katz et al., 2010). The No-Go N2 is a fronto-centrally generated negativity arising between 200 and 400 ms, and the No-Go P3 is the later positive potential arising between 400 and 600 ms (Smith et al., 2008). The No-Go N2 is thought to reflect conflict monitoring mechanisms, while the No-Go P3 is a more direct reflection of motor inhibition (Katz et al., 2010; Smith et al., 2008; De Sanctis et al., 2012, 2013; Donkers and van Boxtel, 2004; Nieuwenhuis et al., 2005; Enriquez-Geppert et al., 2010; De Sanctis et al., 2014).

ERP measures associated with performance monitoring are also well defined. When participants fail to withhold a response, a negativity occurs approximately 50–100 ms after the error is made. This negativity is referred to as the Error-Related Negativity (ERN) (Holroyd and Coles, 2002). A subsequent slow wave that follows the ERN at approximately 120–400 ms is referred to as the error-related positivity, or the Pe. The ERN is thought to reflect a conflict monitoring signal, denoting cortical registration of an incorrect response execution (Holroyd and Coles, 2002). The Pe has been shown to reflect subsequent error awareness (O'Connell et al., 2007). Additionally, in order to explore the effect of anhedonia and determine whether it is associated with more severe substance abuse outcomes, we collected self-report information about trait and state anhedonia, as well as information about addiction severity (Chapman et al., 1976; McLellan et al., 1985; Franken et al., 2007b).

We hypothesized that current cocaine abusers would demonstrate reduction in task accuracy, reduced post error slowing, and attenuation of ERP components related to inhibition, performance monitoring and error awareness. Furthermore, impairments would be correlated with addiction severity. We also hypothesized that the degree of executive impairment would be correlated with trait anhedonia in both cocaine users and controls. These findings may inform a more comprehensive model of the phenotype of substance dependence that incorporates information about both executive dysfunction and affective dysregulation.

2. Methods

2.1. Participants

For this study, twenty-seven (7 female) control participants with no drug use history were recruited using advertisements on Craigslist and through word of mouth. Twenty-three (7 female) current cocaine abusers were recruited using Craigslist ($N = 14$) and from the Next STEPs programs at Waters Place and Port Morris ($N = 9$), which are outpatient treatment programs located in Wellness Centers in the Bronx and affiliated with the Albert Einstein College of Medicine. The Next STEPs programs are dedicated treatment centers that focus on helping patients achieve abstinence from cocaine and provide outpatient treatment and counseling options. All potential participants were administered the Structured Clinical Interview for the DSM-IV and were also administered screening questionnaires related to their overall physical and mental health. Exclusion criteria for cocaine abusers and controls were as follows: 1) Any DSM IV, Axis 1 diagnosis (excluding dependence or a past diagnosis of depression or dysthymic disorder caused by drug use for the cocaine users); 2) Head trauma resulting in loss of consciousness for longer than 30 min; 3) Presence of any past or current brain pathology; 4) A diagnosis of HIV; 5) Age above 55 years and below 18 years. Because of the high rates of comorbidity of alcohol and drug abuse among the cocaine using population, cocaine abusers were not excluded if they abused other drugs or alcohol. However, cocaine abusers were excluded if cocaine was not their primary drug of choice. Years of drug use were recorded during the screening questionnaires and the addiction severity index (ASI) interviews. Controls were also excluded if they had any major Axis 1 disorder or alcohol/drug dependence diagnosis, including nicotine dependence, or if any first degree family members had an alcohol/drug dependence diagnosis. A urine screen was performed on all participants to test for the presence of metabolites related to cocaine, THC, or opiates. Participants were paid for their participation in the form of one $12 gift card to local department stores per hour of experiment time. All participants signed an informed consent document administered by HIPAA-certified staff. All procedures were approved by the Institutional Review Board of the Albert Einstein College of Medicine and the City College of the City University of New York. The study conformed to the principles outlined in the Declaration of Helsinki.