



# Common and distinct neural correlates of inhibitory dysregulation: Stroop fMRI study of cocaine addiction and intermittent explosive disorder



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## ABSTRACT

Despite the high prevalence and consequences associated with externalizing psychopathologies, little is known about their underlying neurobiological mechanisms. Studying multiple externalizing disorders, each characterized by compromised inhibition, could reveal both common and distinct mechanisms of impairment. The present study therefore compared individuals with intermittent explosive disorder (IED) ( $N = 11$ ), individuals with cocaine use disorder (CUD) ( $N = 21$ ), and healthy controls ( $N = 17$ ) on task performance and functional magnetic resonance imaging (fMRI) activity during an event-related color-word Stroop task; self-reported trait anger expression was also collected in all participants. Results revealed higher error-related activity in the two externalizing psychopathologies as compared with controls in two subregions of the dorsolateral prefrontal cortex (DLPFC) (a region known to be involved in exerting cognitive control during this task), suggesting a neural signature of inhibitory-related error processing common to these psychopathologies. Interestingly, in one DLPFC subregion, error-related activity was especially high in IED, possibly indicating a specific neural correlate of clinically high anger expression. Supporting this interpretation, error-related DLPFC activity in this same subregion positively correlated with trait anger expression across all participants. These collective results help to illuminate common and distinct neural signatures of impaired self-control, and could suggest novel therapeutic targets for increasing self-control in clinical aggression specifically and/or in various externalizing psychopathologies more generally.

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## 1. Introduction

Failures of self-control characterize many neuropsychiatric disorders, manifesting as chronic and relapsing behavioral tendencies that contribute to poor physical and mental health and evoke serious public health concerns. For example, drug addiction is a well-studied neuropsychiatric disorder marked by persistent neurocognitive

dysfunction, including excessive salience attributed to drugs and drug-related stimuli (Luijten et al., 2013), disadvantageous and impulsive decision-making (Paulus, 2007), poor behavioral adaptation (Salo et al., 2009), and dysregulated inhibitory control (Kalivas and Volkow, 2005). Another externalizing disorder, far less studied but similarly marked by behavioral dysregulation, is intermittent explosive disorder (IED). As a clinical disorder, IED is defined by recurrent episodes of aggression and violence in response to disproportionately low provocation (Coccaro, 2004). Such reactive aggression has been associated with high emotional arousal in tandem with poor cortically-mediated response inhibition to halt a

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prepotent aggressive tendency (Raine et al., 1998; Siever, 2008). Thus, here we focus on both addiction and IED as clinical entities marked by Impaired Response Inhibition and Salience Attribution (iRISA) (Goldstein and Volkow, 2002, 2011), an empirically supported and theoretically-bound model of addiction that has mapped core self-regulatory dysfunction onto aberrant corticostriatal circuitry. Studying both of these externalizing disorders can provide novel neurobehavioral signatures of compromised inhibitory control, which have the potential to enrich our understanding of a broad spectrum of neuropsychiatric disorders characterized by iRISA.

To focus our efforts in this initial study, we concentrated on response inhibition. Participants performed an event-related color-word Stroop task (Stroop, 1935), a classical cognitive paradigm of conflict- and error-related processing, while undergoing functional magnetic resonance imaging (fMRI). This task consistently engages select prefrontal cortical subregions that participate in response inhibition and cognitive control, including the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Carter and van Veen, 2007; Kerns et al., 2004; MacDonald et al., 2000; Roberts and Hall, 2008) – regions that are also perturbed in addiction and aggression. Indeed, numerous studies have documented abnormalities in the ACC and DLPFC as underlying core neurocognitive dysfunctions in drug addiction (Goldstein and Volkow, 2011). These regions also show reactivity to laboratory aggression challenges in healthy individuals (Denson et al., 2009; New et al., 2009). Importantly, a meta-analysis revealed functional and structural deficits of the right ACC and left DLPFC [and the orbitofrontal cortex (OFC)] in aggressive/antisocial individuals compared with healthy individuals or psychiatric controls (Yang and Raine, 2009). Specifically, the color-word Stroop task (and related Stroop task variants) has been previously used to probe the functioning of the ACC, DLPFC, and other regions comprising the frontoparietal network, tapping into the core phenomenology of drug addiction as further associated with clinical outcome (Barros-Loscertales et al., 2011; Brewer et al., 2008; Devito et al., 2012; Mayer et al., 2013; Moeller et al., 2014a; Worhunsky et al., 2013). However, we are not aware of any prior studies that used the color-word Stroop task in IED, an understudied impulse control disorder.

Here, we hypothesized that group differences [i.e., between healthy controls versus individuals with IED and/or individuals with cocaine use disorder (CUD)] would emerge in PFC regions that are typically engaged by the color-word Stroop task, and that are impaired in these psychopathologies (e.g., ACC, DLPFC). Based on our prior experience (Moeller et al., 2014a), we expected especially robust PFC group effects during error-related processing (i.e., instead of Stroop conflict processing), whereby a more optimized (i.e., reduced) response would characterize the healthy controls versus IED and CUD. We further expected that IED and CUD would show comparable hyperactivity of these regions, possibly indicating a common neural signature of compromised inhibitory/PFC functioning. Finally, beyond comparing IED and CUD, we also probed for regions that would uniquely track pathological aggression (i.e., abnormal activations specific to IED) – regions that we further hypothesized would correlate with trait anger expression.

## 2. Methods

### 2.1. Participants

Participants were 17 healthy controls, 11 individuals with IED, and 21 individuals with CUD, recruited from local newspaper- and website advertisements, and by word-of-mouth. All were male, right-handed, native English speakers, not currently taking medications, and able to understand all study procedures and provide written consent in accordance with Stony Brook University's Institutional

Review Board. Exclusion criteria were: (A) history of head trauma or loss of consciousness (>30 min) or other neurological disease of central origin (including seizures); (B) abnormal vital signs; (C) history of major medical conditions, encompassing cardiovascular (including high blood pressure), endocrinological (including metabolic), oncological, or autoimmune diseases; (E) contraindications to MRI; and (F) except for cocaine in CUD, positive urine screens for psychoactive drugs or their metabolites (10/21 CUD participants tested positive for cocaine on the day of scanning). Eleven participants (7 controls, 4 IED, 0 CUD) were drawn from a study (unpublished) during which they received a single-dose challenge of methylphenidate or counterbalanced placebo during fMRI (for details of methylphenidate administration, and analyses showing this procedural difference did not drive our effects, see [Supplementary Data](#)). None of the study participants demonstrated or endorsed signs or symptoms of intoxication from alcohol (determined by breathalyzer) or cocaine (determined by trained study staff).

Participants underwent a comprehensive clinical interview, consisting of: (A) Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996; Ventura et al., 1998); (B) Addiction Severity Index (ASI) (McLellan et al., 1992); (C) Cocaine Selective Severity Assessment Scale (Kampman et al., 1998); (D) Severity of Dependence Scale (Gossop et al., 1992); (E) Cocaine Craving Questionnaire (Tiffany et al., 1993); (F) Structured Clinical Interview for Axis II personality disorders, specifically of Cluster B; (G) assessment for Intermittent Explosive Disorder, which enables IED diagnosis according to DSM-IV criteria (Coccaro, 2004); and (H) Life History of Aggression, which tallies the amount of aggressive behavior across the lifespan (Coccaro et al., 1997). Because components F–H were not administered to this sample of CUD (i.e., these procedures were not yet in place for these individuals), alternative measures/interviews were examined in their stead (see [Supplementary Data](#) for these measures and analyses, which provide evidence that these CUD were dispositionally non-aggressive).

Based on this interview, all IED participants met criteria for intermittent explosive disorder (current:  $N = 7$ ; remitted:  $N = 4$ ), all CUD participants met criteria for cocaine use disorder (current:  $N = 17$ ; remitted:  $N = 4$ ) (Table 1, which also shows that the groups did not differ on remission status), and no IED participants met criteria for cocaine use disorder. We allowed IED into the study who had comorbid substance use disorders (SUDs), which occurred for 4/11 IED, because of the high overlap of these two disorders in the general population (approximately 35% in adults) (Kessler et al., 2006), enhancing generalizability of our results; nevertheless, we accounted for the presence of comorbid SUDs in the [Supplementary Data](#). Also of importance, IED and CUD did not differ on current or lifetime comorbidities (Table 1) (see [Supplementary Data](#) for specific comorbidities in each group). No controls met criteria for either disorder, which is an important consideration for comparison purposes (i.e., we did not expect IED and CUD to differ from one another, but both psychopathologies to differ from controls). Across all groups, 27 participants had a history of smoking, and 23 participants were current smokers (Table 1).

### 2.2. fMRI

#### 2.2.1. Task

Participants performed three runs of an event-related fMRI color word Stroop task, which has been described in detail elsewhere (Moeller et al., 2014a, 2014b, 2012). Briefly, participants pressed for ink color of color words printed in their congruent (94% of trials) or incongruent colors (6% of trials, spaced by  $\geq 5$  congruent stimuli). Each word was presented for 1300 ms, with an intertrial interval of 350 ms. Remuneration for task completion was \$25. Accuracy and reaction time (RT) were continuously collected.

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