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Machine-learning identifies substance-specific behavioral markers for opiate and stimulant dependence

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ABSTRACT

Background: Recent animal and human studies reveal distinct cognitive and neurobiological differences between opiate and stimulant addictions; however, our understanding of the common and specific effects of these two classes of drugs remains limited due to the high rates of polysubstance-dependence among drug users.

Methods: The goal of the current study was to identify multivariate substance-specific markers classifying heroin dependence (HD) and amphetamine dependence (AD), by using machine-learning approaches. Participants included 39 amphetamine mono-dependent, 44 heroin mono-dependent, 58 polysubstance dependent, and 81 non-substance dependent individuals. The majority of substance dependent participants were in protracted abstinence. We used demographic, personality (trait impulsivity, trait psychopathy, aggression, sensation seeking), psychiatric (attention deficit hyperactivity disorder, conduct disorder, antisocial personality disorder, psychopathy, anxiety, depression), and neurocognitive impulsivity measures (Delay Discounting, Go/No-Go, Stop Signal, Immediate Memory, Balloon Analogue Risk, Cambridge Gambling, and Iowa Gambling tasks) as predictors in a machine-learning algorithm.

Results: The machine-learning approach revealed substance-specific multivariate profiles that classified HD and AD in new samples with high degree of accuracy. Out of 54 predictors, psychopathy was the only classifier common to both types of addiction. Important dissociations emerged between factors classifying HD and AD, which often showed opposite patterns among individuals with HD and AD.

Conclusions: These results suggest that different mechanisms may underlie HD and AD, challenging the unitary account of drug addiction. This line of work may shed light on the development of standardized and cost-efficient clinical diagnostic tests and facilitate the development of individualized prevention and intervention programs for HD and AD.

1. Introduction

Drug addiction is typically regarded as a unitary phenomenon (Badiani et al., 2011); however, animal and human studies increasingly suggest that despite their many similarities, different classes of drugs such as opiates and stimulants have distinct mechanisms of action and neurobehavioral correlates (Badiani et al., 2011; George and Koob, 2010; Verdejo-García et al., 2007). Both classes of drugs modulate the dopamine (DA) system but the mechanisms of these modulations differ for opiates and stimulants (Kreek et al., 2012) and there is surprisingly minimal overlap of genes associated with these classes of drugs (Kendler et al., 2003; Tsuang et al., 1998). Moreover, recent studies provide little support for a general liability factor to substance misuse and instead reveal that liability to misuse illicit substances is substance-specific (Clark et al., 2016). There are major differences in the role of the ventromedial prefrontal cortex (vmPFC), which appears to serve fundamentally different roles in opiate and stimulant addictions, acting as a neural OFF switch for cocaine seeking, but an ON switch for heroin seeking (Peters et al., 2013). A growing number of preclinical studies similarly reveal that opiate and stimulant addictions have dissociable effects with opiates producing inhibitory and sedative effects, in contrast to stimulants' arousing and excitatory effects (Badiani et al., 2011; Stewart et al., 1984). Further, trait impulsivity predicts greater stimulant intake, but not heroin intake (Dalley et al.,

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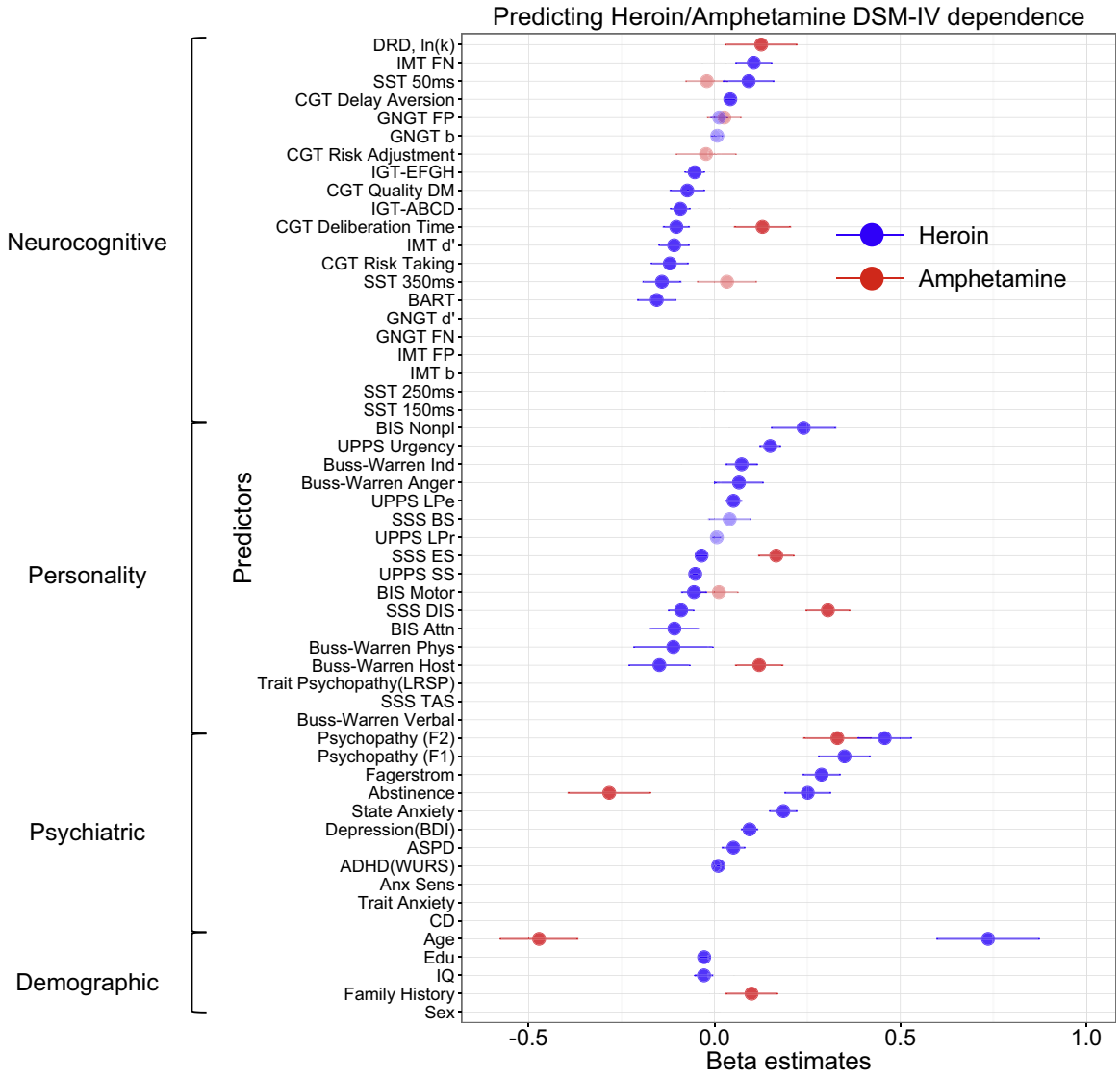

Fig. 1. Multivariate patterns of demographic, psychiatric, personality, and neurocognitive measures classifying individuals with past heroin- or amphetamine-dependence. CD = Conduct Disorder; ASPD = Antisocial Personality Disorder; BDI = Beck Depression Inventory; Anx = Anxiety; Anx Sens = Anxiety Sensitivity; LRSP = Levenson's Self-Report Psychopathy Scale; PCL = Psychopathy Checklist: Screening Version; WURS = Wender Utah Rating Scale for ADHD; BIS = Barratt Impulsiveness Scale; SSS = Sensation Seeking Scale; IGT = Iowa Gambling Task; SST = Stop Signal Task; IMT = Immediate Memory Task; DRD = Delayed Reward Discounting; BART = Balloon Analogue Risk Task; GNGT = Go/Nogo Task; CGT = Cambridge Gambling Task; DA = Delay Aversion; DT = Decision Time; QDM = Quality Decision-Making; RA = Risk Adjustment; RT = Risk Taking.

2007; McNamara et al., 2010). Also, both clinical and preclinical studies reveal that the differential effects of these drugs depend on the specific environmental context, with the sedative effects of opiates being greater in familiar and non-arousing environments, whereas the rewarding effects of stimulants are enhanced in novel and arousing environments (Caprioli et al., 2008).

However, clinical studies of personality and neurocognitive factors show mixed findings that are inconsistent with preclinical studies. For example, both opiate and stimulant users report increased trait impulsivity (Stanford et al., 2009) and sensation seeking (Ersche et al., 2010). Clinical studies of neurocognitive function also show mixed results: some studies report distinct patterns of neurocognitive performance in opiate and stimulant users (Ornstein et al., 2000; Rogers et al., 1999; Verdejo-García et al., 2007) whereas others report comparable neurocognitive profiles (Kirby and Petry, 2004).

There are three major gaps in the existing clinical literature on opiate and stimulant addictions that we aim to address in this work. First, as previously noted (de Wit, 2008), despite the overwhelming preclinical and clinical evidence supporting *impulsivity* as a key factor of potential etiological significance for virtually all types of addictions, impulsivity is multidimensional and few studies have concurrently assessed its multiple personality, psychiatric, and neurocognitive dimensions in users of different classes of drugs (c.f., Vassileva et al., 2014). Most previous studies (Ahn et al., 2014b; Kirby and Petry, 2004; Rogers et al., 1999) have typically focused on a single or a limited number of measures (c.f., Whelan et al., 2014); however, evidence suggests that specific dimensions of impulsivity may be differentially related to different aspects of addictive behaviors. For example, urgency (i.e., acting impulsively during negative emotional states) has been associated with substance related problems whereas sensation seeking has been associated with frequency of substance use (Castellanos-Ryan and Conrod, 2011; Cyders et al., 2009; Smith et al., 2007). Further, mounting evidence indicates that some dimensions of impulsivity may be potential endophenotypes for drug addiction (Kreek et al., 2005) and meet endophenotype criteria (Bickel, 2015; MacKillop, 2013); however, the relative predictive utility of these

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