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Sensitization-based risk for substance abuse in vulnerable individuals with ADHD: Review and re-examination of evidence

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Abstract

Evidence of sensitization following stimulants administration in humans is just emerging, which prevents reaching more definitive conclusions in favor or against a purported protective role of stimulant treatments for ADHD for the development of substance use disorders. Existing evidence from both animal and human research suggest that stimulants produce neurophysiological changes in the brain reward system, some of which could be persistent. This could be relevant in choosing optimal treatments for young patients with ADHD who have additional clinical risk factors for substance abuse (e.g. conduct disorder (CD) and/or familial addictions). Here we stipulate that, while the majority of youth with ADHD greatly benefit from treatments with stimulants, there might be a subpopulation of individuals whose neurobiological profiles may confer risk for heightened vulnerability to the effects of stimulants on the responsiveness of the brain reward system. We propose that focused human research is needed to elucidate the unknown effects of prolonged stimulant exposure on the neurophysiology of the brain reward system in young patients with ADHD.

Introduction

Considerable data demonstrate that psychostimulant medications significantly improve cognitive and behavioral function in youth with attention-deficit/hyperactivity disorder (ADHD) (Cortese et al., 2020). In particular, two classes of stimulants (methylphenidate and amphetamines) have been well established as effective first line treatments (though some countries recommend use of methylphenidate first, and some do not allow the use of AMPH (Raman et al., 2018)). However, neuropharmacological research also suggests that stimulant medications have abuse liability (Kollins et al., 2003) and indeed are abused and diverted (Faraone et al., 2020). Consequently, stimulants are designated Schedule 2 controlled substances by the US Drug Enforcement Administration. There has also been considerable discussion regarding the effects of stimulant medications on the developing central nervous system, primarily because treatment with stimulant medication can be considered to represent exposure to an abusable substance (Kollins 2003, Huskinson et al., 2014). Moreover, chronic stimulant administration in adolescence has been shown to cause brain structural changes in rodent models (van der Marel et al 2014). One significant concern is that exposure to stimulants early in life might sensitize the brain to the subsequent

exposure to drugs of abuse, increasing the risk for substance use disorder (SUD). However, this 'sensitization model' has been primarily developed from animal studies (see section below). The situation with respect to humans has been unclear.

In this review, we consider sensitization in humans – specifically, the extent to which exposure to stimulants early in life could sensitize the brain to subsequent exposure to drugs of abuse such that the probability of developing a SUD in adolescence and adulthood is increased. We will review data suggesting increased SUD risk due to sensitization as well as evidence indicating that stimulants protect *against* the development of future SUD. We posit that mixed findings regarding SUD risk from stimulant treatment may stem from differences between studies on the incidence of either comorbid psychopathology, with resultant variability in response to stimulants (protective vs neutral or deleterious) in relation to subsequent SUD, or underlying neurobiological factors common for both ADHD and SUD that may confer vulnerability for SUD development. We argue that more research on the potential multiplicity of outcomes with treatment is needed, including a greater understanding of which children may be at risk for sensitization effects and possibly elevated SUD risk. We conclude that sensitization is NOT a problem for the majority of youth with ADHD treated with stimulants, but we also consider the possibility that there is a subgroup of children who are at relatively elevated risk for SUD, and for whom the phenomenon of sensitization may be relevant.

Methods

We conducted a focused evaluation of published studies in the following areas of research: 1) studies of the phenomenon of sensitization in general, and particularly the role of stimulants in producing behaviors indicative of sensitization in both animals and humans; 2) the purported role of overlapping clinical and neurobiological characteristics that underlie the relationship between ADHD, considered itself a risk factor for SUD, and other factors contributing to the development of SUD in adolescence; and 3) the effects of stimulant treatment on phenotypical and neurobiological outcomes in individuals with ADHD. Therefore, we considered experimental studies analyzing the effects of stimulants on the brain reward system in both animal and human research as well as large scale longitudinal and epidemiologic studies assessing clinical outcomes of stimulant treatment in ADHD cohorts.

As a first step we performed a computerized research to identify all relevant studies in PubMed from January 1980 up to September 2021 using the following search terms: "sensitization", "stimulants", "dopamine", "neurotransmitters", " stimulant treatment", ADHD, "substance use disorders", SUD risk", "neuroimaging", "brain reward system", "hypo-activation, "hyper-activation", "reward anticipation", "reward notification". Each of these search terms produced a list of studies that reported on animal and human experimental studies examining sensitization effects. As this work builds on a hypothesis that has not been tested, we did not intend to produce a systematic review but to present a theory of possible sensitization effects in humans - and make a case for future research directions on a topic that has not received much attention in human research but may have potentially important clinical implications including treatment selection for youth with

ADHD. Therefore as a second step we selected the most relevant studies from the initial list of papers that may have supported or opposed the main premises of this review."

What is sensitization and why might it matter?

The term "sensitization" has generally been used to describe a phenomenon wherein repeated exposure to an abusable drug elicits progressively increasing behavioral, neurocircuit, or neurotransmitter response to that same drug (Steketee & Kalivas 2011) on repeat exposure. For example, repeated intermittent exposure to psychostimulants can lead to dysregulation of mesolimbic DA signaling (Kalivas et al., 1986, Robinson et al., 1987) that, in turn, may lead to hyperlocomotion (Laruelle., 2000, Featherstone et al., 2007) or drug-induced psychosis (Angrist & Gershon 1970). It is argued that repeated exposure to an abusable substance results in changes in synaptic neurotransmission or second-messenger signaling in regions linked to motivation and information processing of rewarding stimuli, which in turn might "sensitize" the brain to increase risk for the development of substance use or abuse (Adinoff, 2007).

Sensitization paradigms studied in animal models have indeed shown that exposure to AMPH leads to physiological and morphological changes in the brain's reward system, including increased dopamine (DA) release in the mesolimbic system (Robinson et al., 1982; Robinson & Becker, 1986; Kalivas & Stewart, 1991; Robinson & Berridge, 1993; Nestby et al., 1997; Pierce & Kalivas, 1997; Kantor et al., 1999; Vanderschuren et al., 1999; Schrantee et al., 2017). One study reported 3–5 week enhancement of cue-elicited DA release from striatal tissue following a single injection of 1.25 mg/kg of AMPH (Robinson et al., 1982), while others reported increased DAD1 receptor sensitivity in the NAcc (Henry & White, 1991; White & Kalivas, 1998) and increased length and number of dendrites in the nucleus accumbens (NAcc) and increased number of pyramidal neurons in the prefrontal cortex (Robinson & Kolb, 1997, 1999). Further, studies have shown that sensitization of midbrain DA neurons with AMPH was associated with the development of AMPH self-administration (Vezina., 2004), that exposure to AMPH and stress similarly resulted in enhanced predisposition to AMPH -taking behavior (Piazza et al., 1990) and that after a 3-week extinction period AMPH can reinstate drug-seeking behaviors developed by self-administration of other drugs like heroin and cocaine (De Vries et al., 1998). Moreover, studies using the other stimulant class, methylphenidate (MPH), have also documented that pre-treatment results in enhanced self-administration of abusable substances such as nicotine (Wooters et al., 2008), cocaine (Brandon et al., 2001) and methamphetamine (Baladi et al., 2014) in rodent models (see next section for details).

Cross-sensitization in animal models

A variation on this model is "cross-sensitization", wherein exposure to one drug could sensitize the brain to other drugs that share certain properties or mechanisms in common. Most preclinical experiments have examined the extent to which early life exposure to non-stimulant drugs, particularly Δ−9-tetrahydrocannabinol (THC), increases subsequent drug self-administration of "harder" drugs. For example, exposure to THC in adolescent rats is associated with higher levels of heroin self-administration in adulthood (Ellgren

et al., 2008). Notably, adolescent exposure to THC in rats significantly increases the propeptide precursor gene Penk mRNA expression levels in the NAcc shell. This suggests that disturbances of the enkephalin reward system due to early THC exposure may have long lasting effects – a finding that has been replicated in humans as well (see Boileau et al., 2006). Reports by Spano et al. (2007) and Tomasievisz et al. (2012) further link adolescent THC exposure to disruptions in the developmental pattern of methylation, indicating that epigenetic dysregulation of Penk underlies the long-term effects of THC. The relevance of this research to the current discussion is grounded in: i) evidence showing that THC administration enhances striatal DA levels (Malone & Taylor, 1999; Tanda et al, 1997), and ii) reports documenting changes in the expression of Penk in rats after repeated cocaine self-administration, as well as linkages between increased expression of Penk in D1 and D2 containing neurons in the Nacc in rats with compulsive methamphetamine self-administration (Przewloka et al.,1995, Crespo et al., 2001). Taken together, these reports support the thesis that substances with abuse potential such as THC and stimulants (e.g. cocaine and methamphetamine), despite different chemical structures and molecular targets, share the ability to upregulate the expression of certain genes that can further produce persistent neuroadaptations in brain regions involved in the process of incentive motivation and reward, thus making these regions hypersensitive to the hedonic effects of other drugs (Robinson & Berridge, 1993).

Summary

Animal studies have provided evidence of sensitization by stimulants (and THC) at the behavioral and neural levels, and (with respect to gene expression) of opioid receptors. Moreover, the animal data indicate that these physiological effects of sensitization can be sustained for extended time periods. Specifically, the animal data support the suggestion that early life exposure to stimulants may create changes in the brain reward system that would facilitate increased drug self-administration (e.g. nicotine, cocaine, methamphetamine) later in life. We now consider the data from work with human participants.

Evidence supporting sensitization in humans

Paralleling the early animal work showing “sensitization” by stimulants (repeated exposure leading to hyperlocomotion), Strakowski et al. (1996), in a double-blind, placebo-controlled study, gave drug-naive participants two treatments of 0.25 mg/kg AMPH 48 hours apart and reported that, compared to the first treatment, the second treatment elicited significantly greater increases in four behavioral measures: activity/energy, mood, rate and amount of speech and eye-blink rate. In a second study, Strakowski & Sax (1998) extended these findings by showing that two behavioral measures (e.g. activity/energy and eye-blink rate) increased progressively with repeated administration.

With respect to sensitization of the brain’s motivational circuitry, data show that drugs of abuse, including stimulants, share the property of increasing extracellular DA preferentially in the NAcc (DiChiara 2002). It is argued that these supraphysiologic surges of DA in the NAcc provide the reinforcing effects of substances of abuse, given the similarity to the phasing firing of DA neurons which also results in a very fast increase of DA

(Owesson-White et al., 2009). Although sparse, data from human imaging studies also show that sensitization protocols can elicit changes in the brain motivational neurocircuitry. For instance, Boileau et al., (2006) gave healthy adult participants 3 doses of AMPH (dextroamphetamine sulfate, 0.3 mg/kg by mouth) administered on days 1, 3, and 5 and recorded DA release in response to AMPH by PET and [11C]raclopride on days 1 & 5 and 1 year later. Consistent with a sensitization-like phenomenon, the second and third PET scans showed increased DA release (i.e., greater reduction in [11C]raclopride binding) relative to the initial dose in the ventral striatum, progressively extending to the dorsal caudate and putamen. O'Daley et al (2014) used a similar design with 22 adult male participants in an attempt to detect signs of sensitization via fMRI scanning. In this study the researchers used a double-blind procedure, and the subjects received the first 3 doses of AMPH or placebo with a 48-hour inter-dose interval (sessions 1–3) and then received a 4th dose after a two week wash-out period (session 4). Participants were scanned approximately 120 minutes post-drug/placebo administration during sessions 1 (acute exposure) and 4 (repeated exposure) while performing a working memory task, a motor learning task and a rewarded gambling task. The results suggest that repeated AMPH exposure is associated with reduced dorsal striatal BOLD signal during decision making, but enhanced ventromedial caudate activity during reward anticipation. This latter finding may reflect enhanced DA release, in that reward cue-elicited activation in ventromedial caudate has been shown to correlate with individual differences in phasic DA release ascertained via PET (Schott et al., 2008, Buckholtz et al., 2010).

With respect to potential behavioral manifestations of sensitization (i.e., an increased risk for subsequent substance use), some data indicate that sensitization of the midbrain DA neurons with dopaminergic agents (such as levodopa) increases the risk that patients may develop behavioral "addictions" or escalated drug use. For instance, levodopa administration in patients with Parkinson's disease has been linked to compulsive gambling and risky sexual behaviors (Cools et al., 2003). Moreover, PET imaging has documented enhanced striatal DA release in patients chronically treated with levodopa who had developed compulsive drug-seeking behavior (Evans et al., 2006) or pathological gambling (Steeves et al., 2009).

Summary

Human data, like the animal data, indicate that repeated administration of AMPH can increase movement (Strakowski et al, 1996, Strakowski & Sax, 1998; Kessler et al., 2006). Studies with adult humans have also revealed sustained changes in DA/brain reward responsiveness following repeated administration of AMPH (Boileau et al.,2006; O'Daley 2014). There are also indications of behavioral consequences of sensitization by levodopa, indexed by addictive types of behaviors (e.g., gambling, risky sexual behaviors and drug seeking; (Cools 2003, Evans 2006, Steeves 2009)). As such, animal and human data suggest that prolonged treatment by stimulants could lead to sensitization in patients with ADHD. In the following section, we review the literature on the associations between ADHD, SUD and stimulant treatment.

ADHD and SUD risk

Data indicate relatively high rates of comorbid ADHD and SUD (Kessler et al., 2006; Wilens, 2006; Kollins, 2008: Zulauf et al., 2014). Approximately 15% of adolescents and young adults with ADHD have a comorbid substance use disorder (SUD), while 11% of individuals with an SUD also meet criteria for ADHD (Galan & Humphreys, 2017). Notably, a recent report from the MTA study found that participants with ADHD, relative to those without, showed higher rates of weekly marijuana use (32.8% ADHD vs. 21.3% LNCG) and daily cigarette smoking (35.9% vs. 17.5%), a greater incidence of early substance use in adolescence (57.9% ADHD vs. 41.9% controls), younger first use of alcohol, cigarettes, marijuana, and illicit drugs, and a slightly faster escalation in substance use in early adolescence (Molina et al., 2018). Studies have documented that ADHD confers an increased risk for alcohol use disorder as well as for nicotine, marijuana or cocaine substance use disorders (Lee et al., 2011). The World Federation of ADHD international consensus statement indicates that ADHD patients are 50% more likely to develop a drug, alcohol or nicotine- related disorders compared to unaffected individuals (Faraone et al., 2021). Notably, a diagnosis of ADHD typically precedes the emergence of substance use by 6 to 8 years; i.e., ADHD represents a risk factor for SUD rather than the other way around. However, it has also been suggested that there might be a bidirectional relationship between these disorders across the lifespan; i.e., not only is ADHD associated with an increased risk for SUD but SUDs may exacerbate ADHD symptomatology (Kessler et al., 2006; Zulauf et al., 2014).

It is important to note, however, that some have argued that the association between ADHD and SUD primarily reflects an association between comorbid oppositional defiant (ODD) or conduct disorder (CD) and SUD (Pingault et al., 2013). In line with this, some studies have reported that the association between ADHD and SUD is no longer significant once the association between SUD and ODD/CD is controlled for (Yoshimasu et al., 2016). However, it should be noted that other studies have reported a significant association between ADHD and SUD even *after* associations with ODD/CD are accounted for (Groenman et al., 2017). Of course, adopting the RDoC framework, focusing on circuit-level transdiagnostic neurobehavioral features (Cuthbert & Insel, 2013), may reduce focus on comorbidity when the core relevant phenotype is poor behavior regulation. Indeed, there are data indicating shared underlying neurobiological vulnerabilities (e.g. shared genetic liability (Vilar-Ribo et al., 2021)) that are seen in patients with ADHD, CD and SUD. For instance, both ADHD and SUD have been characterized as disorders of hypodopaminergic neurotransmission, which may be linked to disrupted response control/inhibition and reward processing (Ivanov et al., 2008). As ADHD has its onset in early childhood it may follow that individuals showing disruption in these functions are also at increased risk of the future development of SUDs (Slobodin et al., 2015). Below, we review potential neurobehavioral mechanisms for ADHD-related liability to SUD, in terms of aberrant incentive-motivational “approach” neurocircuity, as well as deficits in inhibitory circuit function, which may curtail reward-related impulses.

Response control/inhibition:

A series of studies have documented that patients with ADHD show behavioral impairment on response control/inhibition tasks such as the go/no-go task, the stop-signal task (SST) and the Stroop task, where reaction-time variability (indicative of sporadic inattentiveness) may be a more prominent feature than increased commission errors per se (Koffler et al., 2013). Regions consistently implicated in response control/inhibition (i.e., dorsomedial frontal and inferior frontal/anterior insula cortices and dorsal striatum; e.g., Aron et al., 2016) also show atypical recruitment in children and adolescents with ADHD relative to controls on inhibitory control tasks (Smith et al., 2006; Hart et al., 2013). Notably, inhibition deficits (Yuong et al., 2016: McTeague et al., 2016) and blunted recruitment by these regions in inhibitory control tasks (Hwang et al., 2009; McTeague et al., 2017) have been found in adolescents with conduct problems/CD – though they appear to be more highly associated with ADHD symptomatology than aggression per se, even in these participants (Young et al., 2009; Hwang et al., 2016). Indeed, it has been argued that inhibitory control deficits may be common to all mental illness (Caspi & Moffit, 2018).

With respect to substance use, developmental studies have shown that hypo-activation in brain regions associated with response inhibition is associated with later problematic substance use. For example, 12–14-year old participants who transitioned into heavy alcohol use over 4 years displayed blunted neural activation during no-go trials of a go/no-go task at baseline in frontal, parietal, and temporal cortices and striatum (Norman et al., 2011). Similarly, 11–16 year old substance-naïve participants who went on to heavy drinking within three years also showed blunted no-go elicited activation in the bilateral middle frontal gyrus, right inferior parietal lobule and left striatum during no-go trials relative to abstainers (Wetherill et al., 2013). Other work has also found blunted ventromedial frontal cortex recruitment prognostic of youth drinking (Mahmood et al., 2013) and cannabis abuse in girls (Spechler et al., 2018). Finally, atypical signaling of Bayesian prediction errors (i.e. the difference between actual and expected need to stop on a given trial) within rostral medial and anterior insula cortices as well as striatum developmentally predicted problematic stimulant use (Harle et al., 2015).

Reward responsiveness:

Anticipation activity reflects expected value, the individual’s expectation of the value of the reward to come, and is critical for successful decision-making (Clithero & Rangel, 2014). Receipt activity reflects the achieved reward and may be modulated by prediction error (the difference between the received and expected reward) and is critical for future learning. Negative prediction errors (following expected reward > received reward) down-regulate the reward response. Positive prediction errors (following expected reward < received reward) up-regulate the reward response (Clithero & Rangel, 2014).

Clinical neuroscience work has indicated that reward responsiveness during anticipation or receipt can be differentially disrupted in patients. With respect to patients with ADHD, studies have relatively consistently revealed that anticipatory striatal reward response is attenuated (see reviews Plichta & Scheres, 2014 and Grimm et al., 2021). However, there have also been reports of increased reward response in patients with ADHD relative to

comparison individuals within striatum (von Rhein et al., 2015) and orbitofrontal cortex (Rubia et al., 2009; Tegelbeckers et al., 2018). This discrepancy may owe to the critical role of the ventral striatum in mobilizing attention and other cognitive effort itself (which can falter in ADHD), even in the absence of reward or a contrast in expected value (Boehler et al., 2011). Tepid recruitment of motivational neurocircuitry by effortful reward prospects coupled with exaggerated response to received rewards could introduce a bias toward low-effort activities with a high hedonic payoff—such as binge substance use.

Similarly, work with adolescents with conduct problems/CD has generally indicated reduced reward responsiveness (Rubia et al., 2009; Zhang et al., 2021; Hawes et al., 2021; Finger et al., 2011) with some exceptions (Bjork et al., 2010). Moreover, notable recent work from the Adolescent Brain Cognitive Development (Bjork et al., 2017) sample has suggested that this reduced reward responsiveness may, like in patients with ADHD, be particularly marked for reward anticipation while responsiveness to reward receipt may even be exagerated (Hawes et al., 2021). With respect to the response to punishment, there have also been several reports of atypical (often elevated) responses to punishment in youth with ADHD classified as having “high risk” for SUD, most often defined as having comorbid ODD/CD or familial SUD (Finger et al., 2008; Crowley et al., 2010; White et al., 2013; Byrd et al., 2014 & 2018; Bjork & Pardini, 2015; Hulvershorn et al., 2015; Tenebaum et al., 2018; Ivanov et al., 2019). One particular report has suggested that increased striatal responses to punishment (or at least a failure to down-regulate responding following punishment) in youth with CD (White et al., 2013).

In general, the relationship between nondrug reward-elicited brain activation and risk for substance use disorder is complex and context specific (Bjork, 2020; Blair, 2020). There have been suggestions that increased reward responsiveness predicts future substance abuse. This is supported by one report showing that increased striatal BOLD responses (caudate and putamen) to the receipt of monetary rewards at age 15 predicted substance use onset (alcohol, nicotine, marijuana, stimulants and others) 1 year later (Stice et al., 2013). Another study examined two cohorts (one aged 8–13 years and another aged 18–23 years; combined N=175) and found that increased NAcc activation to reward anticipation was positively associated with the number of alcohol-related problems reported over the next 3–6 years, after controlling for lifetime drinking at time of the scan (Heitzeg et al., 2014). One report (Carey et al., 2017) suggests that polygenic risk for ADHD is positively associated with increased reward responsiveness in the striatum (most likely mediated by DA) and problematic alcohol use, which is consistent with the hypothesized common role of DA in reward processing in both ADHD and SUD. In contrast, another group found no significant relationship between VS activation to reward and prediction of early alcohol abuse using a variant of the same Monetary Incentive Delay task (Nees et al., 2012). Several studies based on the IMAGEN dataset also failed to support the suggestion of increased reward responsiveness as a risk factor for substance abuse. Moreover, they all reported that hypoactivation during reward related responses was associated with increased drug use (Whelan et al., 2014, Butchell et al., 2017, Ivanov et al., 2021).

Summary.

ADHD and SUD show a high degree of co-morbidity even if the emergence of ADHD developmentally precedes substance use by a number of years. This may reflect the fact that forms of neuro-cognitive dysfunction identified as underpinning ADHD appear also to be neuro-cognitive risk factors for the emergence of substance use, which may have a common genetic diathesis (Edwards & Kendler, 2012). These forms of neuro-cognitive dysfunction relate to non-optimal response control/inhibition and dysfunctional reward/punishment processing. While stimulant treatment overall improves ADHD symptoms and to some extent measures of disinhibition it is also possible that a sub-cohort of ADHD individuals may have either suboptimal or altogether different response to stimulants, particularly in relation to altered reward processing. In the next two sections, we consider studies examining the impact of stimulant treatment for patients with ADHD with respect to: (i) future substance use/the development of substance use disorders; and (ii) brain function, to potentially inform a critical risk/benefit analysis of stimulant use with respect to substance use risk, perhaps specific to some populations or clinical scenarios.

Naturalistic studies of stimulant treatment for ADHD

If ADHD were to confer risk to SUD by virtue of alterations in reward and inhibitory processing, it stands to reason that pharmacological rectification of these phenotypes would reduce incidence of SUD. Moreover, improved cognition may induce follow-on indirect benefits on reducing environmental risk for SUD in that improved academic performance may deter stimulant-treated youth from falling into deviant peer groups (cite). Naturalistic longitudinal studies in children with ADHD have been utilized to ascertain whether stimulant treatment in early life alters the probability of SUD development in later life. However, these types of studies have produced mixed results, with some showing protective effects of stimulants (Biederman et al., 1999; Wilens et al., 2003, 2008), especially if treatment was started at a younger age (Manuzza, et al., 2008), others showing risk-conferring associations (Lambert & Hartsough., 1998; Lambert 2005) and others showing no association (Humphreys et al., 2013; Molina et al., 2013, 2007; Harty et al., 2011; Biederman et al., 2008). For example, one study, with predominantly male youths (N=208) obtained from the Danish psychiatric registers, reported the relative risk (RR) of SUD and alcohol abuse was 7.7 (4.3–13.9) for cases with ADHD and 5.2 (2.9–9.4), for comparison youth (Dalsgaard et al., 2014). Factors associated with elevated risk for SUD were female sex, conduct disorder in childhood and *older* age at initiation of stimulant treatment. A second, and the largest study conducted so far, used the Swedish national registers and followed up all individuals born between 1960 and 1998 diagnosed with ADHD (26,249 men and 12,504 women; Chang et al., 2014). The authors found no indication of increased risk of substance abuse among individuals prescribed stimulant ADHD medication. Rather, the data suggested a long-term protective effect with respect to the development of substance abuse. Consistent with these studies, a recent review reported that the data largely indicated negative associations between previous stimulant treatment and treatment duration and subsequent SUD when compared to no treatment (Chang et al., 2019).

The above illustrates the difficulty in elucidating the complex relationship between ADHD, stimulant treatment and SUD. Naturalistic studies have several inherent limitations that complicate determination of the risk for development of SUD following stimulant treatment. For one thing, ADHD is itself a risk factor, and people who are treated with stimulants almost always have ADHD. Additionally, there are a host of variables that likely differ across individuals, and about which there is insufficient information – e.g., dosing and length of treatment, treatment compliance, comorbid conditions (Molina et al., 2013). We posit that one critical source of variability in these studies is that they differ in the proportion of participants in whom stimulant use may be problematic (such as due to vulnerability to sensitization). For example, some studies of youth with ADHD may under-recruit "high risk" individuals for a variety of reasons. For instance, the MTA sample (aged 7–10 years at study entry) had very low rates of comorbid CD (e.g. 8%) at study entry, which is considerably lower than the rates reported by the CDC (i.e. up to 50% of youth diagnosed with ADHD may show symptoms of comorbid CD, although this is mostly true for teens https://www.cdc.gov/ncbddd/adhd/data.html). Further, cohorts recruited for longitudinal studies are not large enough to separate comparable groups of youth with ADHD only vs. youths with ADHD and comorbid ODD or CD and/or familial SUD. With respect to epidemiological natural-history surveys, the prescription of stimulants to youth with some degree of behavioral problems is not random, and may be over-represented in the most strongly-affected youth, making comparisons of outcomes between prescribed vs non-prescribed children more difficult.

Moreover, the collection of accurate data on medication use and compliance with treatment is realistically beyond the scope of any naturalistic study. As a result, the coding of medication treatment is often defined as a binary variable (e.g. Yes vs No; or more often, adequate vs inadequate, with no clear definition of what adequate should be) and the duration of treatment is measured in duration of time treated, but not in cumulative medication used (here, the MTA Study was a notable exception). Similar limitations apply to large scale pharmacoepidemiology studies; for instance it is not always possible to identify "high risk" individuals and it is difficult to establish compliance with medication treatment. Further, clinical trials that focus on the efficacy of stimulant treatment have documented their positive long term effects (e.g. for period longer than 12 weeks, Maia et al, 2017), however, these time intervals are often too short to meaningfully examine any effects on SUD development since substance misuse and problem use develop over much longer time periods. In short, the proposition that a subgroup of individuals who present with particular combinations of clinical risk factors (e.g., ADHD+CD) may be uniquely affected by treatment with stimulants cannot be sufficiently tested using data from longitudinal naturalistic or pharmacoepidemiology studies. Therefore, it is not surprising that the existing literature provides very limited information on possible differences in clinical outcome as a function of treatment in selected subgroups of individuals with ADHD at high vs low risk for SUD independent of treatment experience.

Instead, Robinson and Berridge (2000, 2008) have argued that it is critical to index changes in the neurobiological underpinnings of reward processing in response to stimulant exposure as an objective measure of possible sensitization. Data on the brain level changes in patients with ADHD following stimulant treatment will be considered in the next section.

Effects of Stimulant treatment in ADHD on Brain Activation

As noted, there are considerable data demonstrating that psychostimulant medications significantly reduce symptoms in youth with attention-deficit/hyperactivity disorder (ADHD) (Cortese et al., 2018). Notably, treatment with stimulants significantly "normalizes" the neuro-cognitive dysfunction associated with ADHD, with potential benefits in terms of normative school function and relatedly reduced potential to fall in with deviant peer groups. A systematic review of this literature, examining inhibitory control, attention and working memory task performance, reported that single dose MPH was associated with increased activation within frontal lobes, striatum, and cerebellum in youth with ADHD (Czerniak et al., 2013). The increase in activation within dorsomedial and inferior frontal cortex during response control/inhibition tasks was most evident. There were also clear indications that MPH increased striatal responsiveness – however as no studies using reward tasks were included in that review the effects of MPH specific to reward processing were not examined (Czerniak et al., 2013).

While there are reports documenting that MPH can reduce choice impulsivity related to reward preference (Campez et al., 2021) there is a dearth of evidence examining the effects of stimulants on brain activation during reward processing - with the exception of one report from 13 drug-naïve ADHD children and matched controls (Rubia et al., 2009a). This last study reported that MPH down-regulated the ADHD patients' observed heightened orbitofrontal response to reward receipt.

Summary:

Longitudinal, naturalistic studies of the association between ADHD treatment with stimulants and risk for the development of SUDs have been inconclusive, though recent registry studies point to a protective rather than a risk-conferring role (Chang et al., 2019). Studies examining the brain response to reward in patients with ADHD following prolonged stimulant treatment have not been conducted. However, there are indications of increased striatal functioning following stimulant treatment, albeit for non-reward tasks (Czerniak et al., 2013).

Our review of the literature on baseline abnormalities in ADHD indicate that when compared to unaffected counterparts, ADHD youth predominantly exhibit hypoactivation in widely distributed brain networks. However, there are reports suggesting that ADHD may be associated with hyperactivation, that such hyperactivation may be observed during particular task conditions (e.g. punishment), and in individuals with ADHD and comorbid disruptive behavior disorders or with familial SUD (who can also be defined as high risk for SUD). While there are fewer studies looking at changes in brain activation pre to post stimulant treatment (predominantly with a single dose of stimulant instead of prolonged treatment), available reports suggest that stimulants tend to "normalize" baseline abnormalities of activation in either direction – meaning to increase it when there is hypoactivation and to decrease it in cases of hyperactivation (Rubia et al., 2009). Considering these possibilities, we suggest the following directions for further investigations in reward processing in ADHD as it may relate to possible sensitization effects of stimulant treatments.

Suggested directions for systematic research on individual differences in risk for psychostimulant sensitization

There are two clear directions for research given the options outlined above. First, while it does appear that patients with ADHD generally show reduced striatal responses to reward (see reviews by Plichta & Scheres, 2014; Grimm et al., 2021), it is still possible that either certain sub-groups (e.g., those with ADHD and CD, or ADHD with callous-unemotional traits (Hawes et al, 2021)) and/or specific individuals with ADHD show *heightened* striatal responses to reward. As such, it would seem critical to determine reliable indices for individual-level assessments of reward responsiveness. Of course, concerns regarding the test-retest reliability (TRR), and thus the clinical utility, of neuropsychological and fMRI tasks used with psychiatric patients has been recently raised (Elliott et al., 2020; Hedge et al., 2017). However, simulation re-analyses have determined recommendations that reduce/remove these concerns; i.e., increasing the number of trials per condition and not using contrast-based analyses (e.g., Chen et al., 2021; Haines et al., 2020; Rouder and Haaf, 2019). A focus on developing age-appropriate measures of reward sensitivity with excellent psychometric properties needs to be a priority. The development of such measures may help determine the extent to which heightened, or reduced, reward responsiveness is a risk factor for the development of substance use disorders. The ABCD project may help in this regard, and particularly to determine the extent to which heightened reward responsiveness, and its association with sub-clinical impulsivity (see Plichta and Scheres, 2014), may be a risk factor for substance use even if reduced reward responsiveness is a risk factor the development of substance use *disorders* (Blair, 2020).

Second, there is a clear paucity of data on the impact of treatment (vs challenge) with stimulants (and also non-stimulants) on reward processing in patients with ADHD and associated conditions. This research is challenged by the confounding of stimulant effects on reducing head motion in the scanner itself, which may artifactually improve detected activations by reducing noise (not from any neurocircuit or ligand-related effects). While there are indications that stimulants change striatal responsiveness in patients with ADHD, the striatal responsiveness was not to reward (Czerniak et al., 2013). Behavioral data demonstrate changes in reinforcement sensitivity in patients with ADHD following treatment with stimulants but the neuro-cognitive basis of this remains unknown (Campez et al., 2021). It will be important to determine whether stimulants “normalize” striatal responsiveness to reward in patients with ADHD and/or whether specific doses convey a risk for “over-responsiveness” such that impulsive choices, including decisions to engage in substance use, are increased. Notably, data confirming that non-stimulants show a significantly reduced impact on reward responsiveness in patients with ADHD relative to stimulants would be important to confirm. Interestingly, emerging animal studies have provided preliminary evidence that non-stimulants can reduce drug self-administration (Jordan et al., 2014) and prevent the development of compulsive behaviors (Ansquer et al., 2014). The development of compulsivity is considered to be an essential part of the SUD syndrome. This may suggest a potential protective role of non-stimulant treatment, in the context of ADHD, on reinforcement processing.

Concluding remarks

In summary, although the research on psychostimulant sensitization in humans is limited, the available evidence suggests that repeated exposure to psychostimulant drugs can produce lasting changes in the activation of the brain reward system. Based on our conceptualization of the existing evidence in relation to activation patterns of the brain reward system characteristic of ADHD, as well as activation patterns of the brain reward system associated with SUD risk and changes in activation following administration of stimulants we consider two main scenarios related to possible sensitization. First, the majority of data on the relationship of stimulant treatment of ADHD and SUD outcomes suggest neutral and indeed potentially protective effects (Chang et al., 2019). This may relate to the baseline abnormalities in ADHD indicating that, when compared to unaffected counterparts, ADHD youth exhibit predominantly hypoactivation in wide distributed brain networks related to both response control and (anticipatory, in particular) reward processing (Plichta & Scheres, 2014; Grimm et al., 2021). The literature on developmental risk for SUD tends to point towards more clinically severe cases being associated with an increased risk for the development of SUD when: (i) behavioral control is disrupted (Plichta & Scheres, 2014); and (ii) reward responsiveness in the striatum and the orbitofrontal cortex is reduced (Whelan et al., 2014, Buchel et al., 2017, Ivanov 2021). As such, stimulant treatment in patients with ADHD may be protective as it serves to increase phasic dopamine function and thus both buttress response control (Czerniak et al., 2013) and potentially increase reward responsiveness; i.e., reduce two neurobiological risk factors for the development of SUD.

Second, it is worth noting that there may be subgroups of children who are at particularly elevated biological and environmental risk for SUD (i.e. related to clinical factors such as comorbid psychiatric disorder(s), and/or psychosocial factors, or familial SUD) for whom the phenomenon of sensitization may be relevant. For example, the childhood disorder most associated with an increased risk for the development of SUDs is Conduct Disorder (CD) (Disney et al., 1999; Flory & Lynam, 2003; Masroor et al., 2019), which is highly co-morbid with ADHD (Spencer, 2006). It has been argued that patients with co-morbid ADHD/CD might show increased reward responsiveness (possibly related to reward outcomes instead of anticipation) and that this puts them at risk for the development of SUDs (Bjork & Pardini 2015; Tenenbaum et al., 2018; Hawes et al., 2021). While most data indicate hypo-reward responsiveness for both youth with ADHD and with other disruptive behavior disorders (Rubia et al., 2009; Zhang et al., 2021; Hawes et al., 2021; Finger et al., 2011; Crowley et al., 2010), this possibility cannot be discounted – particularly when the largest study to date indicated hypo-responsiveness to reward anticipation but hyper-responsiveness to reward receipt (Hawes et al., 2021). It is possible that stimulant treatment for these individuals might exacerbate the brain reward system's response to future drug taking, potentially increasing risk for SUD development. Alternatively, there are indications both that general impulsivity in typical developing individuals is associated with increased reward responsiveness (Hariri et al., 2006; Plichta and Scheres, 2014) and that increased reward responsiveness predicts substance use onset (Stice et al., 2013; Heitzeg et al., 2014). In cases when stimulant might have a paradoxical effect on impulsivity (i.e. increasing instead of

decreasing impulsive behaviors) this may further amplify the activation in the brain reward system and in turn may also exacerbate risk for future SUD in these individuals.

Theoretically, there is the possibility that in some individuals stimulants - even when used in recommended doses - may have unusual effects on the brain reward system and may cause over-activation in regions that show baseline hypo-activation. In other words, a subset of youth with ADHD who exhibit the conventional hypoactive response to rewards still may be considered at risk if their response to stimulants is abnormal. Since there is no evidence to show any consistent patterns of stimulant response by the brain reward system in ADHD it is imperative to direct future studies in the venue of pairing clinical trials of stimulants (and non-stimulants) with sensitive and validated neuroimaging paradigms to comprehensively assess the pre- to post – treatment (not single dose challenge) changes in the neurophysiology of the brain reward system.

In order to disentangle these complicated relationships, we suggest that targeted studies in carefully defined risk groups that probe intermediate phenotypes offer a feasible and cost-effective first pass approach. Also required for illumination of these issues is a greater understanding of how attentional effort itself relates to mesolimbic recruitment by reward prospects in the MID task and similar reward tasks (such as if both hedonic-related signals and top-down attention-related signals additively drive VS activation), and how this relationship may differ with ADHD. It stands to reason that it is essential to evaluate sensitization at the neurobiological level by the use of fMRI– with the conclusion that individuals with the most pronounced signs of sensitization will be most at risk for developing SUD. These predictions are testable, and appear to be most relevant to “high” risk individuals (i.e. youth diagnosed with ADHD and comorbid ODD/CD, and/or family history of SUD, in addition to showing a particular imaging signature of activation/connectivity within the brain reward system), who may be exposed to abusable agents via treatment with stimulants to control symptoms of their disruptive behavior disorder(s). Optimally, a combination of longitudinal and experimental studies will provide definitive answers as to whether stimulants may facilitate the development of SUD in individuals defined as “high risk”, or whether stimulants and non-stimulants may both have protective effects in “high risk” individuals. Such research would not only advance our understanding of the relationship between ADHD and SUD, but it may provide crucial information to assist practitioners in their decision making about the use of stimulants in high risk populations.

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