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## ADHD, Altered Dopamine Neurotransmission, and Disrupted Reinforcement Processes: Implications for Smoking and Nicotine Dependence

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### INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) affects millions of children and adults in the US and is a significant independent risk factor for smoking (Kessler et al., 2006; Lambert & Hartsough, 1998; Milberger et al., 1997a; Milberger et al., 1997b; Molina & Pelham, 2003; Pomerleau et al., 1995; Visser et al., 2007). Individuals with ADHD start smoking at an earlier age and become more dependent (Milberger et al., 1997a; Wilens et al., 2008). Moreover, individuals with ADHD or high levels of ADHD symptoms are also more likely to progress from smoking experimentation to regular use (Rohde et al., 2004). For example, we found that high levels of ADHD symptoms in a population-based sample were associated with progression from experimentation or no use in the teenage years to daily smoking in the early 20s (Fuemmeler et al., 2007). Given the extraordinary morbidity and mortality associated with cigarette smoking (CDC, 2002), the high rate of smoking observed among those with ADHD is therefore a significant public health issue. A clearer understanding of the factors that increase risk for smoking in those with ADHD would be an important step towards preventing and treating smoking in this high-risk group.

The association between ADHD and smoking is complex and involves multiple stages (McClernon & Kollins, 2008), although the precise mechanisms conferring risk have not been thoroughly elucidated. Convergent evidence suggests that dopamine-mediated disruptions in reinforcement processes are involved in key aspects of smoking behavior among individuals with ADHD. The overall goal of the present review is to consider the evidence for the role of dopamine and reinforcement processes in increased risk for smoking and related outcomes in patients with ADHD. The review will be organized as follows. First, we will review both historical and current perspectives on the role of dopamine functioning

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in ADHD. Second, we will consider evidence implicating disrupted reinforcement processes in ADHD. We will then discuss the few studies that have explicitly linked dopaminergic dysfunction to altered reinforcement processes in ADHD. The relevance for this association to understanding smoking risk in individuals with ADHD will then be evaluated. We will conclude with suggestions for future research in this area.

## **DOPAMINE AND ADHD**

### **Historical Perspectives on Catecholamine Function in ADHD**

For decades, researchers and clinicians have speculated about the role of disrupted neurotransmission and subsequent reinforcement processes as key features of ADHD. Paul Wender, an early pioneer in the study of ADHD and its treatment, wrote in 1973 that Minimal Brain Dysfunction (MBD; a nosological precursor to ADHD) was “characterized by...a diminished sensitivity to positive and negative reinforcement,” and “...that these deficits are secondary to disorders of monoamine metabolism and that such disorders may occur on a genetic basis”(Wender, 1973). This reasoning was supported by several clinical and scientific observations: 1) MBD and related problems were likely to run in families; 2) stimulant drugs were effective for improving behavior problems in children with MBD and related difficulties (Bradley, 1937); and 3) that these same drugs facilitated monoamine neurotransmission in animals (Schildkraut & Kety, 1967; Wender et al., 1971). In the 40 years since Wender’s prescient speculation, significant progress has been made that provides support for his hypotheses. We will briefly consider the evidence for the genetic basis of ADHD (with emphasis on genes associated with dopamine neurotransmission) and the direct measurement of dopamine neurotransmission in individuals with ADHD.

### **Genetic Studies of ADHD – Links to Dopamine Function**

As Wender noted, it has long been observed that problems associated with ADHD run in families. Family, twin, and adoption studies all provide strong support for the genetic basis of the disorder, with heritability estimates from twin studies as high as 0.7-0.8 (Faraone et al., 2005). Since the mid-1990s, several hundred candidate gene studies have been conducted to isolate specific variants conferring risk for the disorder. Although these studies have often been characterized by small effect size and failures to replicate, several gene variants have consistently been shown to increase risk for ADHD. Perhaps not surprisingly, most of these candidate genes are involved in catecholamine function generally, and dopamine function specifically. In one meta-analysis, seven candidate genes were identified that demonstrated significant pooled odds ratios for conferring risk for ADHD across at least 3 separate studies. Of these, 5 of the genetic variants were explicitly involved in dopamine neurotransmission: 2 variants of the dopamine D<sub>4</sub> receptor gene (DRD4), the dopamine D<sub>5</sub> receptor gene (DRD5), the dopamine transporter gene (DAT) and the dopamine beta-hydroxylase gene (DBH) (Faraone et al., 2005). More recently, a meta-analysis specifically focused on dopamine receptor genes (D1-D5), found associations between variants of the DRD4 gene, the DRD5 gene, and the dopamine D<sub>2</sub> (DRD2) gene and risk for ADHD, although due to heterogeneity, findings for the DRD2 gene were deemed to be invalid. (Wu et al., 2012). Although genome-wide linkage and association studies of ADHD have generally not found evidence for the involvement of regions relevant to dopamine

neurotransmission (Faraone & Mick, 2010), the results of candidate gene studies provide some support for dopamine-related genes as contributors of risk, albeit small, for the development of ADHD.

**Functional Role of Dopamine Gene Variants Implicated in ADHD**—Although the functional role of specific dopamine gene variants implicated in ADHD has been partially characterized in nonhuman species and in vitro, work in humans more limited. The most common variant of the DRD4 gene associated with ADHD is a VNTR polymorphism in exon III of the gene, specifically a 7-repeat polymorphism. This variant has been shown to cause a blunted dopaminergic response as compared to other (eg., 4-repeat, 2-repeat) variants (Asghari et al., 1995; Van Tol et al., 1992). In humans, the 7-repeat variant of DRD4 has been linked to differences in ventral striatal activity during reward tasks (Forbes et al., 2009; Nikolova et al., 2011).

The DRD5 gene is expressed widely in CNS and has a significantly higher affinity for dopamine than the DRD1 gene, despite strong similarity in membrane structure (Wu et al., 2012). In general, the DRD5 gene is thought to modulate hypothalamic function and aspects of motor control (Apostolakis et al., 1996; Rivkees & Lachowicz, 1997; Sibley, 1999). The specific functional role of the variant that has been associated with ADHD – a 148-bp allele located in 18.5 kb at the end of the 5' flank – is not known (Wu et al., 2012).

Variations in the dopamine transporter gene (DAT1/SLC6A3) have been implicated in striatal dopamine function in both human and in vitro studies, though findings are somewhat mixed (Heinz et al., 2000; van de Giessen et al., 2009; VanNess et al., 2005). The 10-repeat variant of a VNTR polymorphism in the 3' untranslated region of the gene is most often implicated in the presentation of ADHD, and some studies have reported that 9-repeat carriers of this variant express higher levels of striatal dopamine, while other studies have reported that 10-repeat carriers express more DAT (Heinz et al., 2000; VanNess et al., 2005). Animal models that either knock down or knock out the DAT transporter altogether present with many ADHD-like phenotypes, including increased activity levels that are normalized to wild type levels with stimulant administration (Gainetdinov et al., 1999; Giros et al., 1996; Zhuang et al., 2001).

The DBH gene is involved in the enzymatic pathway that controls the conversion of dopamine to norepinephrine. Several mutations of this gene have been shown to result in DBH deficiency, a relatively rare condition in which low levels of norepinephrine cause difficulty regulating blood pressure and other autonomic nervous system problems (Senard & Rouet, 2006). The specific variant of the DBH gene most widely studied in ADHD is a TaqI polymorphism in the 5<sup>th</sup> intron (Daly et al., 1999; Faraone et al., 2005). Although this variant has been reported to confer risk for other psychiatric/behavioral conditions (e.g., smoking, schizophrenia) (Freire et al., 2006; Wei et al., 1998), the specific function of this polymorphism has not been reported.

### **Assessing dopamine dysfunction in ADHD**

In addition to progress in the identification of dopamine relevant genetic factors associated with ADHD risk, technological advances in the past 25 years have allowed for more specific

inferences to be made regarding how dopamine and other aspects of brain function are related to the clinical features of the disorder. Early attempts to quantify the role of dopamine and other neurotransmitters in ADHD focused on peripheral measures, such as the excretion of urinary metabolites, and results were mixed (Khan & Dekirmenjian, 1981; Shekim et al., 1982; Wender et al., 1971). Since a number of factors can contribute to the levels of such excreted metabolites, these findings are difficult to interpret vis-à-vis the role of these neurotransmitters in the central nervous system.

Wender lamented 40 years ago that “Currently available techniques do not permit direct assessment of neurotransmitter function in the central nervous system” (Wender, 1973). In the ensuing years, however, a number of neuroimaging techniques have been developed to more directly evaluate brain structure and function. Early studies using magnetic resonance imaging (MRI) reported consistent morphological differences between ADHD patients and control subjects in brain regions known to be richly innervated by dopamine containing neurons (eg., caudate nucleus; Castellanos et al., 1994; Hynd et al., 1993)). Studies using functional MRI also reported differences in activation between ADHD and control subjects in dopamine-rich regions, and showed that stimulant drugs altered the patterns of activation in predictable ways (Rubia et al., 1999; Vaidya et al., 1998).

While MRI and fMRI studies allow for inferences regarding physiological activation in dopaminergic brain regions, Positron Emission Tomography (PET) imaging directly measures dopamine activity by measuring the extent to which the neurotransmitter is displaced by radio-labeled tracers in the working brain. The first study to use PET in patients with ADHD was conducted by Zametkin and colleagues and demonstrated deficits in overall cerebral glucose metabolism in adults with ADHD compared to non-ADHD individuals (Zametkin et al., 1990). One of the first studies to explicitly examine dopamine activity using PET imaging used the radiotracer [fluorine-18]fluorodopa, which allows for the assessment of presynaptic dopamine receptor density, in adults with and without ADHD. Results showed significantly reduced presynaptic dopamine storage in the prefrontal cortex that was significantly correlated with a clinical measure of ADHD symptoms/function (Ernst et al., 1998). Similar findings were subsequently reported in children with ADHD, as well as identifying similar patterns of dopamine storage deficiencies in midbrain regions (Ernst et al., 1999).

A number of subsequent studies have examined the density of dopamine transporter (DAT) in midbrain regions. As noted previously, the DAT gene has been implicated in ADHD and the transporter is known to be a central site of action for methylphenidate. Initial studies were mixed, with some reporting decreased DAT density in ADHD patients compared to controls (Volkow et al., 2007), some reporting increased DAT density (Spencer et al., 2007), and some reporting no differences (van Dyck et al., 2002). Other studies demonstrated increases in dopamine D<sub>2</sub>/D<sub>3</sub> receptor activity in striatal regions in adolescents with ADHD (Lou et al., 2004).

Some of these inconsistencies across PET studies of DAT density could have been related to methodological factors (eg., small sample sizes, use of different radiotracers) or patient characteristics (eg., varying histories of medication use). One of the more recently published

PET studies of dopamine receptor density in ADHD sought to address some of these difficulties by enrolling a relatively large sample of adults with (n=53) and without (n=44) ADHD, who had no previous history of medication treatment (Volkow et al., 2009). Using [<sup>11</sup>C]cocaine and [<sup>11</sup>C]raclopride to image DAT and D<sub>2</sub>/D<sub>3</sub>, respectively, this study reported significant decreases in receptor density for both subtypes in brain regions associated with reward and motivation – nucleus accumbens, caudate, midbrain). Moreover, DAT and D<sub>2</sub>/D<sub>3</sub> density was negatively correlated with severity of ADHD symptoms (Volkow et al., 2009).

Collectively, both genetic and neuroimaging studies in the past 20-30 years have supported early speculation regarding the importance of dopamine activity in the presentation of ADHD. Genetic factors associated with dopamine receptor regulation are consistently associated with ADHD and neuroimaging studies have shown that brain structure and function in dopamine-relevant regions are altered in patients with ADHD.

## ADHD AND DISRUPTED REINFORCEMENT PROCESSES

Although historically, ADHD was conceptualized primarily as a disorder associated with disrupted cognition and executive functioning, (Barkley, 1997), most recent models of the disorder have acknowledged the critical role of motivational and reinforcement processes in the presentation of the disorder (Luman et al., 2010; Johansen et al., 2009; Nigg & Casey, 2005; Sagvolden et al., 1998; Sagvolden et al., 2005; Sonuga-Barke, 2005; Sonuga-Barke, 2002; Tripp & Wickens, 2008; Williams & Dayan, 2005). Although defined in different ways, these models are consistent in theorizing that the behavior of individuals with ADHD is not influenced by motivationally-relevant stimuli in the same manner as non-ADHD individuals. In both theoretical models and empirical studies, the construct of motivation has generally been defined on the basis of how externally imposed consequences differentially influence behavior in those with and without ADHD. Work in this area has generated several consistent and important findings (Luman et al., 2010; Luman et al., 2005).

### Immediately delivered rewards improve the behavior of individuals with ADHD

A number of studies have examined the effects of contingent monetary incentives on the performance of individuals with ADHD (Luman et al. 2005). These studies have been conducted in both pediatric and adult populations, and have examined a range of outcomes. In the majority of studies, immediate and externally-delivered reward improved the performance of ADHD patients, often to a greater extent than non-diagnosed controls (Carlson et al., 2000; Carlson & Tamm, 2000; Dosis et al., 2012; Konrad et al., 2000; Marx et al., 2013; McInerney & Kerns, 2003; Strand et al., 2012). For example, in one recent study, the effects of reward were studied across a range of cognitive tasks in adults with and without ADHD. On measures of attention (reaction time variability on a Continuous Performance Test), impulsivity (Commission errors on a Continuous Performance Test) and time perception, the relative effects of reward on performance were greater for adults with ADHD compared to controls (Dosis et al., 2012). Similarly, in a study with children diagnosed with ADHD, immediately delivered rewards improved performance to a similar degree as a moderate dose of MPH, though performance was still not “normalized” compared to a control group of non-diagnosed children performing the task without

medication or reward (Strand et al., 2012). Also of relevance, a number of studies that have examined the effects of immediate incentives on behavior/performance have also found that these consequences increase self-ratings of task motivation (Carlson et al., 2000; Carlson & Tamm, 2000; Dovis et al., 2012; McInerney & Kerns, 2003; Scheres et al., 2001).

A vast clinical literature also supports the use of immediate and contingent reinforcement as the most effective non-pharmacological approach to modifying the behavior of individuals with ADHD. Recently developed and validated non-pharmacological treatments specifically for adults with ADHD also focus on teaching patients ways to increase motivation or self-deliver rewards for adaptive behavior. (Safren et al., 2010; Solanto et al., 2010) For example, 2 of the 3 core modules of Solanto et al.'s meta-cognitive therapy for adult ADHD involve training patients how to "provide contingent self-reward" and "sustain motivation toward distant goals by visualizing long-term rewards." (Solanto et al., 2010)

### **Delayed Rewards are Ineffective and Reinforcement Learning is Disrupted in ADHD**

Patients with ADHD prefer immediate versus delayed rewards, even if such a choice reduces the overall size of the reward. (Bitsakou et al., 2009; Marco et al., 2009; Rapport et al., 1986; Sonuga-Barke & Taylor, 1992; Sonuga-Barke et al., 1992; Tripp & Alsop, 2001) Individuals with ADHD also exhibit steeper temporal discounting functions, suggesting that the value of delayed rewards diminishes faster as the amount of time until its receipt increases. (Costa Dias et al., 2013; Demurie et al., 2012; Scheres et al., 2010; Scheres et al., 2013) The relative lack of efficacy of delayed reinforcers for those with ADHD is most often interpreted as evidence of impulsivity and it has been demonstrated that methylphenidate, a front line stimulant medication used to treat the disorder, decreases temporal discounting in children with ADHD. (Shiels et al., 2009) Individuals with ADHD also have more difficulty learning to adaptively allocate behavior in order to maximize reinforcement and there is evidence that stimulant drugs improve learning under these conditions (Kollins et al., 1997; Luman et al., 2009a; Luman et al., 2009b; Murray & Kollins, 2000; Tripp & Alsop, 1999). This phenomenon has been studied with a number of different experimental paradigms. A series of elegant experiments using multiple fixed-interval extinction (FI-EXT) schedules of reinforcement demonstrated a number of ways in which the behavior of children with ADHD differed from non-diagnosed children (Sagvolden et al., 1998; Sagvolden, 2000). Importantly, this same experimental arrangement was used to validate behavioral differences between a rat model of ADHD and "control" animals (Sagvolden et al., 1992; Sagvolden, 2000).

Overall, there is clear evidence from the literature supporting a role for altered reinforcement processes in individuals with ADHD. Although some models of the disorder propose that these deficits may be relevant for only a subset of individuals who meet criteria for the clinical diagnosis (Sonuga-Barke, 2003; Sonuga-Barke, 2005), the implications of altered reinforcement processes and learning are evident in day-to-day observations of patients with ADHD. Individuals with ADHD are often observed to persist in maladaptive behaviors despite negative consequences, and are commonly reported to be bored easily – suggesting the reinforcing efficacy of stimuli wanes more quickly for patients than for their non-ADHD peers. Finally, the treatment literature is clear in that salient and immediately



delivered consequences are effective for promoting adaptive behavior in individuals with ADHD.

## LINKING DOPAMINE DYSFUNCTION AND DISRUPTED REINFORCEMENT

It is well known that dopamine neurotransmission is integrally involved with behavioral reinforcement (Aggarwal & Wickens, 2011; Wickens et al., 2007; Wise, 2006), and decades of work have dissected the neurobiological and neuropharmacological mechanisms involved with reward and reinforcement processes. “Incentive salience” is commonly used to indicate the motivational tag assigned to a specific stimulus, driving the appropriate behavior to obtain a reward (Berridge & Robinson, 1998; Berridge, 2007; Robinson & Berridge, 1993). Incentive salience, thought to elicit the the ‘wanting’ component of the reward response, is associated with mesolimbic dopamine release. Dopaminergic projections from the VTA to the nucleus accumbens are associated with the behavioral response to cues that predict an upcoming reward (Kosobud et al., 1994; Yun et al., 2004). In classic reinforcement studies utilizing Pavlovian conditioning, dopamine release at the time of the conditioned stimulus attributes a motivational salience to the CS (de Borchgrave et al., 2002; Shaham et al., 2003; Bindra, 1978). Recent optogenetic work has demonstrated that phasic dopaminergic activity is sufficient to drive behavioral conditioning (Tsai et al., 2009). However, it has been proposed that tonic levels of dopamine mediate the overall vigor of the motivated response (Niv et al., 2007), and along these lines it has been shown that the hippocampal disinhibition of dopamine neurons both increases spontaneous firing and amplifies phasic responses to the external stimulation (Lodge & Grace, 2005; Lodge & Grace, 2006). Thus, both tonic and phasic dopamine release are critical for the attribution of incentive salience.

Projections from the prefrontal cortex also play an important role in regulating the mesolimbic pathway during reinforcement and motivation. Early work in anesthetized animals established a physiological link between prefrontal inputs to VTA and dopamine release in the nucleus accumbens (Murase et al., 1993; Karreman & Moghaddam, 1996; Karreman et al., 1996), and more recent work has implicated these circuits in motivated behavior and reward learning: In humans working to obtain reward, information about expected reward activated VTA only via its effects on the prefrontal cortex (Ballard et al., 2011), a finding echoed in physiological work in behaving animals (Takahashi et al., 2011). Glutamatergic projections from the prefrontal cortex to the VTA are necessary for Pavlovian reward learning (Parker et al., 2011). Together with hippocampally-mediated VTA disinhibition, (Floresco et al., 2001; Grace et al., 2007), prefrontal inputs are also critical for setting tonic dopamine levels in the nucleus accumbens (Taber et al., 1995). Blocking prefrontal glutamatergic transmission to VTA decreases dopaminergic tone (Karreman & Moghaddam, 1996; Karreman et al., 1996) Consequently, prefrontal hypoactivity has the potential to result in overall reduced responsivity to reward-related cues, with potential implications for a broad range of motivated behavior. Schizophrenia patients, another population that exhibits prefrontal dysfunction, are also notably lacking in motivational drive (Barch, 2005; Grace, 1991; Knable & Weinberger, 1997; Weinberger et al., 1986). Prefrontal hypoactivity to natural reinforcers may account for decreased incentive salience in addiction (Volkow et al., 2002a; Volkow et al., 2002b). Together these lines of evidence

strongly imply that prefrontal dysfunction will dysregulate dopaminergic function and thus disrupt reinforcement and motivation.

As noted previously, both altered dopamine function and disrupted behavioral reinforcement processes have been implicated in the pathophysiology of ADHD. However, in spite of these demonstrations and despite progress in characterizing the neural mechanisms of behavioral reinforcement, surprisingly little work has been conducted to link observed problems in dopamine neurotransmission with altered reinforcement processes in individuals with ADHD. One study reported that DAT and D<sub>2</sub>/D<sub>3</sub> receptor density in midbrain region was correlated with scores on a trait measure of motivation, an indirect assessment of reinforcement functioning (Volkow et al., 2011). A related study examined the effects of the stimulant drug methylphenidate on extracellular dopamine release during both an academic task and a neutral task. (Volkow et al., 2004). This study found that methylphenidate increased dopamine release, but only in the presence of the academic task, and also reported that the combination of methylphenidate administration and academic task performance increased ratings of motivation and interest. The authors interpreted these findings as evidence for dopamine-mediated increases in reinforcement salience following methylphenidate administration (Volkow et al., 2004).

A series of other studies have explored brain activation in dopamine-rich regions -- specifically the ventral striatum and related areas -- during a task designed to assess reinforcement/reward processing. Though not without exception, these studies have generally reported that individuals with ADHD exhibit hyporesponsivity compared to non-diagnosed individuals during relevant tasks. Most studies have examined brain activation during the Monetary Incentive Delay task (MID)(Knutson et al., 2001), in which brain activation is measured during both reward anticipation and following delivery. Studies with both adolescents and adults have reported VTA hypoactivation in ADHD patients during reward anticipation(Carmona et al., 2012; Edel et al., 2013; Hoogman et al., 2013; Scheres et al., 2007; Strohle et al., 2008), but see also (Paloyelis et al., 2012; Stoy et al., 2011). In addition to decreased activation during reward anticipation, other studies have showed striatal hypo-responsiveness in ADHD patients compared to controls during delayed reward processing (Plichta et al., 2009); and altered nucleus accumbens functional connectivity that was associated with temporal discounting in patients with ADHD (Costa Dias et al., 2013)

Though challenging to characterize real-time dopamine function in patients with ADHD, more work is needed to link such dysfunction to behavioral deficits in reinforcement processes, including learning. Such work could focus on the extent to which differences in dopamine functioning are related to deficits in clinically relevant endpoints, such as learning and memory. Some studies have shown a significant association between measures of dopamine function and broad band clinical ratings of ADHD symptoms or trait measures of motivation (Volkow et al., 2009; Volkow et al., 2011), but such studies should be extended to include additional measures.



## DOPAMINE, REINFORCEMENT, AND SMOKING RISK IN ADHD

The relationship among dopamine function, reinforcement processes, and risk for smoking among individuals with ADHD is complex, but convergent findings from a number of sources highlight the potential importance of dopamine-mediated reinforcement processes in conferring risk for cigarette smoking and nicotine addiction in patients with ADHD. As reviewed thus far, individuals with ADHD exhibit decreased dopaminergic activity in striatal brain regions that are correlated with symptom severity and impairment (Volkow et al., 2009; Volkow et al., 2011), and also exhibit disruptions in reinforcement processes that are known to be influenced by dopamine activity in the same regions (Luman et al., 2010; Luman et al., 2005; Wickens et al., 2007; Wise, 2006).

Similar brain mechanisms have been implicated in the development and maintenance of nicotine addiction. Preclinical studies have demonstrated that *acute* nicotine administration facilitates dopamine signaling in similar areas of the striatum, including the nucleus accumbens, and these actions underlie the rewarding/reinforcing effects of the drug (De Biasi & Dani, 2011). In contrast, *chronic* nicotine exposure and subsequent acute withdrawal both result in substantial reductions in tonic dopamine activity and associated reward-related brain function (Epping-Jordan et al., 1998; Perez et al., 2012; Zhang et al., 2012). Moreover, nicotine withdrawal following chronic exposure results in enhanced sensitivity of DA release to phasic stimulation, such as with acute nicotine administration (Zhang et al., 2012). Moreover, nicotine has been hypothesized to function behaviorally to enhance the reinforcing effects of non-drug stimuli (Chaudhri et al., 2006; Perkins & Karelitz, 2013).

Figure 1 illustrates a simplified pathway linking genetic variation, alterations in dopamine function and related reinforcement processes, and their association with a range of potential smoking outcomes in individuals with ADHD. To this point, the present review has highlighted the extant literature with respect to how genetic factors influence dopamine function and subsequent behavioral reinforcement processes. We will turn attention now to how some of the steps along this trajectory have been explicitly studied with respect to smoking risk in ADHD. Though no studies to date have systematically evaluated this pathway in a single study, results from several investigations support the relevance of different parts of this pathway.

### Genetic Variation interacts with ADHD to Predict Smoking Outcomes

Two studies have reported that the association between genetic variation and ADHD symptoms specifically predicts smoking outcomes. These studies used data derived from the National Longitudinal Study of Adolescent Health (Add Health), a population-based survey of more than 15,000 young adults (Harris et al., 2006). One study reported that levels of self-reported ADHD symptoms in the presence of specific variants of the DRD2 and Monoamine Oxidase A (MAO-A) genes predicted risk of lifetime regular smoking, defined as ever having smoked daily for 30 consecutive days (McClernon et al., 2008a). Specifically, individuals with high levels of hyperactive-impulsive symptoms who were also homozygous for the DRD2 A2 allele were significantly more likely to be regular smokers. Moreover, among females, high levels of both inattention and hyperactive-impulsive

symptoms, combined with carrying the active allele of the MAO-A gene conferred significant risk for regular smoking (McClernon et al., 2008a).

Another study from the same dataset reported that ADHD symptoms in the presence of gene variants predicted initial reactions to smoking experiences (Bidwell et al., 2012). This study found that individuals with high levels of hyperactive-impulsive symptoms and who were homozygous for the DRD2 A2 allele or who carried a variant of the SLC6A4 (serotonin transporter) gene reported significantly greater pleasant initial reactions to cigarette smoking. Elevated levels of inattention symptoms and variants of the MAO-A and CYP2A6 gene were also significantly related to reports of unpleasant initial reactions to cigarette smoking (Bidwell et al., 2012). These findings suggest that individuals with high levels of ADHD symptoms and specific genotypes may experience initial experiences with smoking in a qualitatively different manner, and this could have substantial implications for predicting risk.

### **Abstinence-Induced Smoking Reinforcement is Different in Individuals with ADHD**

It has been established previously that the reinforcing effects of psychoactive drugs may be different in individuals with and without ADHD (Kollins et al., 2009). A recent study found that following biochemically verified 24-hour abstinence, the reinforcing effects of cigarette smoking are significantly greater in adult regular smokers with ADHD compared to smokers without the disorder (Kollins et al., 2013). Smokers with ADHD in this study worked significantly harder for cigarette puffs compared to money following abstinence and were also more likely to report high subjective ratings of withdrawal symptoms. Combined with other studies showing increased severity of smoking withdrawal in ADHD smokers (McClernon et al., 2008b; McClernon et al., 2011), these findings help explain why individuals with ADHD may have more difficulty quitting smoking compared to those without the disorder (Covey et al., 2008; Humfleet et al., 2005; Pomerleau et al., 1995).

Findings from this study along with other literature reviewed heretofore suggest that individuals with ADHD exhibit alterations in striatal dopamine signaling that are potentially further modified following chronic nicotine exposure. Following acute withdrawal, this hypodopaminergic state is further exacerbated, while increasing the sensitivity of the dopamine system to phasic stimulation, such as exposure to cigarette puffs or cues for smoking (i.e., sensory stimuli). This provides some neurobiological explanation for the findings and highlights the need for additional work to clarify the role of altered dopamine signaling in smoking withdrawal among smokers with ADHD.

### **Reinforcement-Based Interventions Reduce Smoking in Individuals with ADHD**

As noted above, it is well-established that providing immediate and clearly defined rewards contingent on some target behavior can be effective for reducing some of the cognitive and behavioral deficits observed in patients with ADHD. Similar principles of behavioral reinforcement are central to contingency management approaches for reducing smoking and other substance use problems (Ledgerwood, 2008; Petry, 2010; Prendergast et al., 2006). Such treatments typically involve the administration of some kind of reward (eg., money, vouchers, chances for prize drawings, etc.) contingent upon biochemically verified

abstinence from drug use. Only study examined a standard contingency management approach for reducing smoking in individuals with and without ADHD (Kollins et al., 2010). Though this study included non-treatment seeking smokers who were generally unmotivated for long-term quitting, results showed that contingency management substantially reduced daily smoking over the course of 2 weeks. Moreover, smokers with ADHD actually maintained slightly higher rates of abstinence compared to non-ADHD smokers (63% vs. 50%), though this difference was not statistically significant. Moreover, rates of abstinence were achieved in spite of higher levels of self-reported withdrawal symptoms (McClernon et al., 2011). These results underscore the potential importance of reinforcement processes in development of novel interventions for smokers with ADHD since immediate and salient (ie., money) consequences for non-smoking contributed to abstinence in spite of worse withdrawal symptoms.

## CONCLUSIONS AND FUTURE DIRECTIONS

It is evident that ADHD can be characterized, in part, by both disruptions in dopamine function and altered behavioral reinforcement processes. These constructs are also likely to give rise to a range of adverse outcomes associated with cigarette smoking and nicotine dependence in individuals with ADHD. To date, however, relatively few studies have been conducted that mechanistically link levels of analysis to understand how these various genetic, neurobiological, and behavioral processes can be leveraged to develop better approaches to prevention and treatment for smoking among individuals with ADHD. As shown in Figure 1, several studies have started this translational work by linking 1 or 2 levels, but future work needs to fill in the gaps. From a clinical perspective, very few studies have investigated how standard treatment approaches for smoking cessation fare in individuals with ADHD. Two randomized trials of stimulant drug treatment as an adjunct to nicotine replacement therapy reported that drug (extended release formulations of methylphenidate or amphetamine) were no more effective than placebo for maintaining smoking abstinence, though in both trials, smokers with ADHD reduced overall smoking rates (Kollins et al., 2012; Winhusen et al., 2010). The development of additional novel interventions could be informed by a better understanding of how dopamine and reinforcement processes are altered during regular smoking and abstinence in individuals with ADHD. In addition, given the findings that ADHD symptoms interact with genotype to predict initial responses to smoking, it may be possible to identify a priori, those children or young adolescents who are most prone to smoking and target prevention efforts more directly. Overall, the rates of smoking among individuals with ADHD remain significantly higher than the general population and these individuals find it harder to quit once they do start. There is great potential for reducing the public health impact of this comorbidity by continued work to understand the basic mechanisms that underlying such risk.

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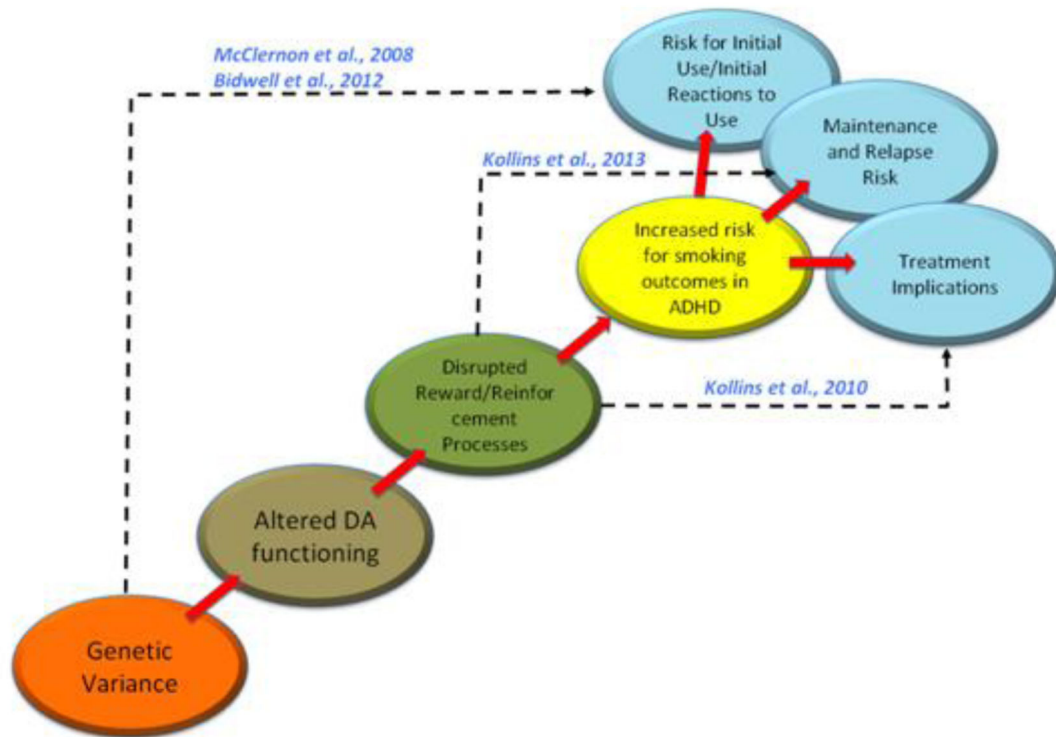
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### Highlights

- ADHD is a risk factor for adverse outcomes related to cigarette smoking
- ADHD is associated with altered dopamine neurotransmission
- ADHD is associated with disrupted reinforcement processes
- Links among dopamine function and reinforcement can help elucidate mechanisms underlying smoking risk in ADHD





**Figure 1.**

Proposed translational trajectory for understanding links among genetic variance, dopamine neurotransmission, altered reinforcement processes, and adverse smoking outcomes in individuals with ADHD. Dotted lines and citations refer to work that has been conducted to link various levels of analysis. These studies are described in more detail in the manuscript.