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Amphetamine-induced dopamine release in treatment-naïve men with ADHD:
A PET/[^{11}C]raclopride study

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) affects up to 10% of school-aged children and half as many adults. The core features of impulsivity, hyperactivity, and inattentiveness commonly give rise to academic underachievement, poor social relationships, and increased risk for mood and anxiety disorders. Although the relevant neurobiological mechanisms remain poorly understood, altered mesocorticolimbic dopamine (DA) transmission has been proposed. The aim of the present study was to compare striatal DA function in treatment-naïve adults with ADHD *vs.* age- and IQ-matched controls. Two PET/[^{11}C]raclopride scans, one with placebo and one with *d*-amphetamine (*d*-AMP; 0.3 mg/kg, p.o.), were administered to five men with ADHD and five healthy male volunteers. The ADHD group differed from controls in demonstrating significant *d*-AMP-induced reductions in posterior caudate ($p<0.05$). These results may support a proposed model of reduced DA tone leading to increased phasic signaling in ADHD.

RÉSUMÉ

Le trouble du déficit de l'attention avec hyperactivité (TDAH) touche jusqu'à 10% des enfants et 5% des adultes. Les aspects centraux du TDAH, soit l'impulsivité, l'hyperactivité, et l'inattention, causent généralement une sous-performance académique, des relations sociales pauvres, et un risque élevé pour les troubles de l'humeur et d'anxiété. Même si les mécanismes neurobiologiques restent incompris, une dérégulation du système dopaminergique mésocorticolimbique a été proposée. Le but de l'étude présente était de mesurer la réactivité du système dopaminergique chez des sujets avec TDAH jamais traités et un groupe témoin du même âge et Q.I. moyen. Deux scans TEP/[^{11}C]raclopride, un avec placebo et l'autre avec la *d*-amphétamine (0,3 mg/Kg administré oralement), ont été effectués chez cinq hommes avec TDAH et cinq bénévoles mâles sains. Le groupe TDAH s'est distingué du groupe témoin en démontrant une réduction des concentrations extracellulaires de dopamine dans le noyau caudé postérieur ($p<0.05$).

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1. INTRODUCTION

1.1 ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

1.1.1 Epidemiology & Phenomenology

Attention Deficit Hyperactivity Disorder is one of the most common childhood conditions, affecting 5-10% of the school-age population (Wolraich et al 1996) and about three times as many males as females (Tannock 1998). The core features of hyperactivity, impulsivity, and inattention give rise to significant academic underachievement and school failure, poor social relationships, lack of motivation, and risk for mood and anxiety disorders.

Close to 85% of children with ADHD continue to have symptoms in adolescence (Barkley 1997). While hyperactivity typically becomes less severe, impulsivity and inattention become relatively more pronounced. There is an increased frequency of school failure and drop out, car accidents, substance abuse, and antisocial behavior with police involvement (Weiss & Hechtman 1993, Barkley et al 1990, Biederman et al 1996). About 50% of children with ADHD continue to have significant problems in adulthood. Again, inattentive and impulsive symptoms predominate and comorbidity is high (Weiss et al 1999).

A recent epidemiological study of 10,000 individuals in the U.S. (Kessler et al 2006) documented that 4% of this adult population met DSM-IV criteria for ADHD. This diagnosis in adults is associated with a great deal of impairment. Compared to age- and gender-matched controls, adults with ADHD have completed less education, have lower job status, more unstable job histories with a high frequency of dismissals and sudden resignations, higher divorce rates, increased risk for serious motor vehicle accidents, and increased rates of substance use disorder, conduct, major depression, anxiety and bipolar disorder (Weiss & Hechtman, 1993, Barkley, 1997a, 1997b, Mannuzza et al 1993, Faraone, 2000).

1.1.2 Neurocognition

Neurocognitive studies suggest that ADHD is associated with deficits in multiple cognitive domains, including vigilance, working memory, response inhibition, temporal processing, and set-shifting (for review, see Castellanos & Tannock 2002; Harvey et al 2004; Seidman et al 2004). Psychological models have emphasized disturbances to executive function, increased sensitivity to rewards, and dysregulated goal-directed behavior and attention to salient events (*e.g.* Douglas 1983; Barkley 1997; Sonuga-Barke 2003). A substantial effect size for inattention between ADHD and controls of 0.52 resulted from a meta-analysis of 17 studies using stop signal, continuous performance, visual search and trail making tasks (Waschbusch 2002). Medium to large effect sizes were also reported in another large meta-analysis for overall cognitive abilities (weighted $d = 0.61$) (Frazier et al 2004). Though most studies have been conducted in children and adolescents, adult ADHD patients, relative to controls, also perform significantly worse on tests of spatial working memory, attention-set shifting and Go/NoGo, consistent with disruption in fronto-striatal pathways functions (McLean et al 2004; Dowson et al 2004).

1.1.3 Functional Neuroanatomy

There is strong support for the involvement of fronto-striatal pathways in the pathophysiology of ADHD. The prefrontal cortex (PFC) is centrally involved in executive functions such as sustained attention and working memory (Miller & Cohen 2001), and the resemblance of ADHD symptomatology to that seen in patients with frontal lobe injuries has been noted (Mattes 1980). In turn, striatal lesions lead to deficits that would be expected from damage to corresponding cortical areas (Divac 1967; Alexandre et al 1986). Sub-compartments of the striatum and their cortical inputs might contribute to different components of ADHD's clinical phenotype. For example, the dorsal striatum plays an important role in voluntary motor responses (Herrero et al 2002). The limbic ventral striatum, in comparison, is implicated in models of ADHD that emphasize delay

aversion and dysregulated attention to emotionally salient events (Sonuga-Barke 1994, 2003; Sagvolden et al 1998).

Volumetric studies of patients with ADHD have identified abnormalities in fronto-striatal circuits with some consistency (for review, see Giedd et al 2001). In affected children, the majority of studies have found reduced striatal tissue volume or reverse asymmetries (Hynd et al 1993; Mataro et al 1997; Castellanos et al 2002; Semrud-Clikeman et al 2000). Decreased prefrontal volume has been found both in ADHD children (*e.g.,* Castellanos et al 2002a; Filipek et al 1997) and in adults (Hesslinger et al 2002).

1.1.4 Dopaminergic Mechanisms

The hypothesis that DAergic mechanisms may play an important role in the pathophysiology of ADHD arises from the clinical efficacy of methylphenidate (MPH), a mixed DA/norepinephrine (NE) transporter blocker, and the observation that the nigro-striatal, meso-cortical and meso-limbic DAergic pathways are implicated in a wide range of behaviors relevant for ADHD.

The clearest role is in the initiation of motor activity (Barbeau et al 1960; Davidson et al 1971; Carlsson 2001), but prefrontal DA transmission has also been shown to play a role in working memory and planning (Brozoski et al 1979; Fuster 1990; Goldman-Rakic 1995; Phillips et al 2004); *i.e.,* the ability to "plan action based on memory" (Seamans & Yang 2004). Low to moderate increases in DA transmission within the PFC enhance executive function, while greater increases are disruptive. Patients with ADHD also exhibit altered reward sensitivity (Douglas 1983; Barkley 1997; Sonuga-Barke 2003), a behavior closely related to the best-studied role of limbic DA transmission (Stewart 1983; Phillips et al 1991; Berridge & Robinson 1997; Wise 2004). Attention, in comparison, is usually considered to be more closely related to NE transmission (Sara & Segal 1991; Aston-Jones et al 1999), but the ability of environmental stimuli to sustain interest may have a significant DAergic component both in cortex and in striatum (Stewart et al 1984; Kapur 2003; Volkow et al 2004; Seamans & Yang 2004).

DA's contribution to these processes is thought to be primarily through its actions as a neuromodulator (Greengard 2001). Recent evidence suggests that the stimulation of D_1 receptors by elevated tonic DA levels diminishes the output of weakly stimulated neurons while enhancing the output of those that are strongly activated, perhaps by keeping them in a depolarized up state in which they more readily fire. In comparison, the stimulation of DA D_2 receptors has been proposed to inhibit post-synaptic cells, making them responsive to strong input only. The overall effect may be to improve signal-to-noise detection, decreasing the salience of irrelevant stimuli (DeFrance et 1985; Nicola et al 2000; O'Donnell 2003). Individuals with ADHD may be suffering from low tonic DA levels resulting in poor signal-to-noise detection and magnified responses to trivial events. Low oral doses of psychostimulant drugs might "normalize" tonic DA levels, accounting in part for their clinical efficacy.

1.1.5 Animal Models

In laboratory animals, features of ADHD can be simulated by DAergic manipulations. In rats, the administration of moderate to high doses of DA agonists induces behavioral hyperactivity. In comparison, impulsive behaviors can be increased by DA receptor antagonists and surgical lesions of the nucleus accumbens (Wade et al 2000; Cardinal et al 2001), while the administration of amphetamines in low doses enhances the ability to choose large delayed rewards over small immediate ones (Cardinal et al 1999; Richards et al 1999; Wade et al 2000).

Animal models of ADHD are controversial, but they also implicate a role of dysregulated DA transmission. The most frequently used model in ADHD research, the spontaneously hypertensive rat (Sagvolden 2000; though see Ferguson 2001), displays motor hyperactivity (Sagvolden et al 1993; Ferguson & Cada 2003), impulsive behavior (Evenden & Meyerson 1999), impaired performance on operant tasks (Wyss et al 1992; Ferguson & Cada 2003), and selective increases in DA function in the posterior mesocorticolimbic DA

pathway (Papa et al 2002) plus hypo-DAergic function elsewhere (Russell et al 1995, 1998). Some of the behavioral disturbances are normalized with stimulant treatment (Myers et al 1982; Sagvolden et al 1992). Decreased DA transmission is also implicated in several other animal models, including the coloboma mutant mouse (Wilson et al 2000) and rats with neonatal 6-OHDA lesions (Shaywitz et al 1976a,b). In comparison, the DAT-KO mouse, a genetically engineered strain with no functioning DAT, and the Naples high excitability rat, both display many of the above cognitive and behavioral characteristics, but have hyperfunctioning DA systems (Giros et al 1996; Jones et al 1998; Gonzalez-Lima & Sadile 2000). These observations underscore the possibility that the diverse neurocognitive and clinical features of ADHD may arise from dysregulations of DA neuro-transmission in multiple subsystems, though both increases and decreases are implicated (Davids et al 2003).

1.1.6 Human Neurobiology

1.1.6.1 Psychostimulants and ADHD

A role of catecholamines in the expression of ADHD has long been suggested by the clinical efficacy of psychostimulant medications, such as MPH and dextro-amphetamine (*d*-AMP). Nearly 200 reports have demonstrated their therapeutic effectiveness, with 70% of patients in clinical trials experiencing significant improvements in inattentiveness and hyperactivity-impulsivity (Spencer et al 1996). Psychostimulants increase extracellular DA and NE levels by a number of mechanisms including the blockade of reuptake by the catecholamine transporters, DAT and NET, and, in the case of amphetamine, facilitating cytoplasmic release by reversing transporter activity. In a sample of healthy adults, a 60 mg oral dose of MPH has been shown to cause a 60% blockade of DAT and a reduction in DRD2 receptor availability by 16%, the latter corresponding to increased synaptic DA levels (Volkow et al 2002).

1.1.6.2 Molecular Genetics

Psychiatric genetics further supports the involvement of DA in ADHD. The majority of twin and adoption studies attribute over 70% of its etiology to genetic factors, and the DA D4 receptor gene (DRD4) has so far been more strongly implicated than any other (Faraone 2004). A meta-analysis of eight studies of the 7-repeat allele of DRD4 revealed an odds ratio of 1.9; that is, the risk of developing ADHD is increased by 90% in individuals carrying this polymorphism. The 10-repeat allele of the DAT gene (DAT1) has also been implicated by a number of studies (for review, see DiMaio et al 2003). The DAT plays an important role in regulating the duration and spatial diffusion of released DA (Cragg & Rice 2004). In individuals with ADHD, striatal DAT levels appear most often increased (Cheon et al 2003; Dougherty et al 1999; Dresel et al 2000; van Dyck et al 2002, but see Volkow et al 2007). Among patients with ADHD, the DAT1 polymorphism has been reported to predict hyperactivity-impulsive symptoms (Waldman et al 1998) and the clinical response to MPH (Kirley et al 2003). Two of three neuroimaging studies suggest that variations in the DAT1 gene predict striatal DAT density (Heinz et al 2000; Jacobsen et al 2000; Martinez et al 2001), while a single study suggests that it does not predict amphetamine-induced DA release (Martinez et al 2001). The negative results might reflect different associations in different populations studied to date (schizophrenia and alcohol dependence) and the poor anatomical resolution of the SPECT [^{123}I]IBZM method (Martinez et al 2001). A small study of ADHD children with (n=7) and without (n=4) homozygosity for the 10-repeat allele revealed an association between homozygosity, increased DAT density, and poor response to MPH treatment (Cheon et al 2005), contradicting the findings of Kirley et al (2003). Recently, a rare DAT coding variant, Ala559Val, was identified in two siblings with ADHD and shown in vitro to be associated with potentiated DAT DA efflux (Mazei-Robinson et al 2008). Remarkably, amphetamine administration blocked this effect, contrary to the enhancement of DAT-mediated DA efflux seen in wildtype DAT. The authors suggest that, though the variant is not a common

polymorphism (it was seen in only two siblings out of the 70 children with ADHD screened), the physiological result could be achieved through a number of polymorphisms in DAT regulatory proteins; it could thus be possible for efflux-competent DAT to be involved in the pathogenesis of ADHD on a population level.

Other genes related to DA activity, such as those for the catecholamine clearance enzymes catechol *O*-methyltransferase (COMT) and monoamine oxidase (MAO), have also been reported to be implicated in the pathophysiology of ADHD, though less consistently (Faraone 2004). In particular, the high-activity COMT $Val^{108/158}Met$ polymorphism has been associated with poorer sustained attention during goal-oriented tasks in children with ADHD (Sengupta et al 2008), yet a recent meta-analysis has shown no association between this polymorphism and an ADHD diagnosis (Cheuk & Wong 2006).

1.1.6.3 DA Synthesis and Metabolism

Cerebrospinal fluid (CSF) levels of homovanillic acid (HVA) are believed to reflect DA metabolism, particularly in the ventral and medial borders of the striatum that are adjacent to the lateral ventricle (Amin et al 1992). Though CSF HVA concentration was first evaluated in people with ADHD nearly three decades ago, agreement has yet to be reached on its relation to the salient aspects of the ADHD phenotype. Two studies reported positive correlations between hyperactivity levels and CSF HVA (Castellanos et al 1994, 1996), with higher CSF concentrations of HVA predicting a superior treatment response to stimulants (Castellanos et al 1996). Yet, there are no known published reports of increased CSF HVA levels in ADHD, relative to healthy controls: two studies reported no patient-control difference (Reimherr et al 1984; Shetty & Chase 1976), while one suggested lower levels (Shaywitz et al 1977). Inconsistent research methods, the possibility of regionally specific effects, and sub-optimal control group selection in these early studies caution against drawing firm conclusions from their results (see Reimherr et al 1984). Recently, though, two

PET/[^{18}F]fluorodopa studies failed to demonstrate evidence of significant differences in striatal DA synthesis in either children or adult patients with ADHD (Ernst et al 1998, 1999).

1.1.6.4 Dopamine Transporter (DAT)

PET and SPECT measurements have been used to investigate DAT density in the brains of children (Cheon et al 2003), adolescents (Jucaite et al, 2005) and adults with ADHD (Dougherty et al 1999; Dresel et al 2000; van Dyck et al 2002, Volkow et al 2007). In the study conducted in adolescents, the age-matching was poor, comparing 13-year old patients to healthy adults who averaged 30 years of age, and a group difference was not seen (Jucaite et al 2005). In one study conducted in adults, a decrease in left caudate and left NAc DAT levels was seen in a treatment-naïve and comorbidity-free group of ADHD patients, relative to age and sex-matched controls (Volkow et al 2007). However, for a given DAT level, a measure of inattention (Conners Adult ADHD Rating Scale, Inattention subscale) was five times greater in the ADHD group compared to controls, suggesting that additional physiological factors may play a significant role in the manifestation of ADHD symptoms. In the remaining four studies, all of which had age-matched control groups, three found significantly increased levels in the affected population, from 16% to 70% relative to healthy controls (Dougherty et al 1999; Dresel et al 2000; Cheon et al 2003). After four weeks of low-dose MPH treatment, DAT binding was decreased by 43% in a group of ADHD adults, with individual reductions correlating well with clinical improvement (Dresel et al 2000). Increased DAT density could reflect increased DAergic innervation or susceptibility to augmented DA clearance, leading to increased *vs.* decreased DA transmission, respectively.

1.1.6.5 D2 Receptor

Three neuroimaging studies have specifically focused on DRD2 binding in drug-free patients with ADHD. Two studies reported evidence of increased DRD2 availability, possibly reflecting low resting synaptic DA levels in ADHD (Ilgin et

al 2001; Lou et al 2004). The higher the DRD2 BP, the poorer the performance on a continuous reaction time task (Lou et al 2004) and the greater the treatment response to MPH (Ilgin et al 2001). The third study, however, found decreased receptor availability in left caudate relative to healthy age-matched controls (Volkow et al 2007). The disagreement could, in part, be due to the mean ages of the ADHD samples investigated, as the first two studies were conducted in children and adolescents, whereas the third tested adults with ADHD.

1.1.6.6 DA Release

Measurement of stimulant-induced DA release has been conducted using the PET / [^{11}C]raclopride method in a pilot study of six adolescents with ADHD (Rosa-Neto et al 2002). It was reported that MPH-induced decreases in [^{11}C]raclopride binding potential (BP) correlated significantly with scores on a behavioral measure of impulsivity; *i.e.,* the higher the impulsivity, the greater that individual's DA cell responsivity. However, interpretation of these data is greatly hampered by the small sample size (n=6) and the absence of a control group. More recently, a second PET / [^{11}C]raclopride study produced contrary results: a sample of nineteen medication-naïve adults with ADHD was found to have depressed MPH-induced DA release in left and right caudate (Volkow et al 2007) compared to 24 age-matched controls. Moreover, greater indices of inattention were associated with smaller reductions in BP in the drug condition.

1.1.7 Other Neurotransmitters Implicated in ADHD

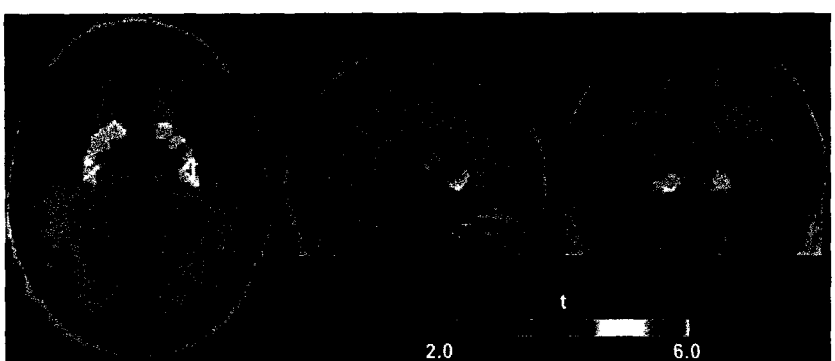
Though DA has received significantly more attention and been more strongly implicated than any other neurotransmitter in ADHD research, it is likely that other systems also play an important role, both independently and through their interactions with DA. For example, the psychostimulant medications that are used to treat ADHD affect NE in much the same way that they affect DA, and pharmaco-therapeutics exhibiting preferential activity at the NET have also exhibited clinical efficacy for ADHD (Solanto 1998; Biederman & Spencer 1999; Christman et al 2004). The mechanism by which they improve ADHD symptoms,

though, remains unclear. In the frontal cortex, the NET is the primary mechanism for clearing DA from the synaptic cleft (Carboni et al 1990; Yamamoto & Novotney 1998), and novel ADHD medications such as the NET blocker atomoxetine increase extracellular levels of both NE and DA in prefrontal regions (for review, see Viggiano et al 2004). Studies evaluating indices of NE, glutamate and serotonin tone and metabolism have also found associations with diagnosis, symptom severity and treatment response (*e.g.* Ernst et al 1997; Carrey et al 2003; MacMaster et al 2003; Courvoisie et al 2004), though this literature is not entirely consistent (for a review of spectroscopic studies of glutamate indices, see Perlov et al 2008). The following study has evaluated DA function uniquely, but in interpreting the results we appreciate that other neurotransmitter systems, particularly those known to modulate DA transmission (e.g. cortico-striatal glutamate), might contribute to ADHD's development and expression.

1.2 MEASURING DA RELEASE IN HUMANS

Neuroreceptor imaging techniques provide a non-invasive method to investigate changes in neurotransmitter concentrations within the human brain *in vivo*. In this regard, the suitability of the PET/[^{11}C]raclopride method for measuring changes in extracellular DA concentrations is now well established (for review see Laruelle 2000).

Due, in part, to its low nanomolar receptor affinity and fast dissociation rate, the benzamide D_3/D_2 receptor antagonist [^{11}C]raclopride is sensitive to competition from endogenous DA within the synapse (Kohler et al 1985). The competitive model (Seeman et al 1989) assumes that changes in endogenous DA synaptic levels are translated into changes in the occupancy or binding potential (BP) of the tracer [^{11}C]raclopride. For example, when a tracer dose of [^{11}C]raclopride



Statistical t-map of areas of significant change in striatal [^{11}C]raclopride binding: 0.3 mg/Kg *d*-amphetamine (p.o.) minus control condition. N = 27 men from healthy populations. Maximum

is administered conjointly or following an experimental procedure that elevates synaptic DA levels, be it a pharmacological challenge (*d*-AMP, ethanol, cocaine, MPH, nicotine, ketamine, psilocybin), an experimental stress challenge (Trier mathematical challenge test) or a cognitive task (video game), measurements of tracer receptor occupancy reveal a reduction in receptor BP, relative to baseline (Volkow et al., 1994; Breier et al 1997; Schlaepfer et al 1997; Vollenweider et al 1999; Koepp et al 1998; Pruessner et al 2000; Leyton et al 2002; Boileau et al 2003). Conversely, depleting endogenous DA (α-methyl-para-tyrosine (AMPT), β-hydroxybutyrate, Reserpine, acute phenylalanine/tyrosine depletion) leaves more receptors available for tracer binding (Ginovart et al 1997; Gatley et al 1997; Leyton et al 2004).

Direct measurements of extracellular DA in primates using *in vivo* microdialysis have established a quantitative relation between *d*-AMP-induced DA release and changes in [^{11}C]raclopride BP, such that a 1% change in BP appears to correspond to a 44% change in extracellular DA (Endres et al 1997; Laruelle et al 1997). In humans endogenous competition studies using *d*-AMP result in observations consistent with the occupancy model: oral and intravenous administrations of *d*-AMP result in a 10% and 15% decrease in BP, respectively (Farde et al 1992; Breier et al 1997; Drevets et al 2001; Leyton et al 2002; Ginovart et al 2004).

Yet, the mechanisms underlying changes in BP in response to changes in synaptic DA concentrations are not fully elucidated, nor are all the data entirely consistent with the occupancy model. It is believed that G-protein-coupled receptor internalization may be involved in the interaction between the radioligand and D_2 receptors: rapid internalization of D_2 receptors in the endosomal compartment in the face of *d*-AMP-induced released DA leads to fewer externalized receptors available for [^{11}C]raclopride binding (Sun et al 2003). Hence, the distribution of receptors in the external and internal pools depends on the relative presence of the agonist. *In vitro* studies have demonstrated the occurrence of agonist-mediated receptor internalization in several transfected cell lines (Barton et al 1991; Vickery & Von Zastrow 1999).

Several methods have been proposed to quantify changes in radioligand-receptor binding. A robust method for yielding parametric images of BP is based on a reference region model that does not require an arterial line for input function. This kinetic model of tracer distribution uses a reference region with negligible binding sites in order to estimate the parameters of interest: BP, R_1, K_2. BP can be expressed as $B_{max} f_2 / K_D^l \left(1 + N_f / K_D^d\right)$, where B_{max} is the total concentration of D_2 binding sites, f_2 the free fraction of radioligand in tissue, K_D^l the equilibrium dissociation constant of the radioligand, N_f the concentration of free DA in tissue, and K_D^d the equilibrium dissociation constant of DA at the D_2 receptor (Gunn et al 1997; Lammertsma et al 1996). A statistical mapping method using this model, that increases sensitivity by increasing the number of degrees of freedom, has been successfully applied (Aston et al 2000).

2. OBJECTIVE AND HYPOTHESIS

Collectively, indirect evidence derived from measurements of various indices of pre- and post-synaptic DA neurotransmission in ADHD patients appear consistent with diminished striatal DA tone coupled with increased stimulant-induced DA release. In this pilot study, we have compared striatal DA release, as assessed with the PET *d*-AMP challenge / [^{11}C]raclopride method, in treatment-naïve adults with ADHD *vs.* age- and IQ-matched controls.

Our working hypotheses, based on the above literature review, were as follows:

1. Relative to age-, sex- and IQ-matched healthy controls, *d*-AMP-induced displacement in [^{11}C]raclopride BP will be significantly elevated in treatment-naïve ADHD patients.
2. Across groups, the degree of *d*-AMP-induced displacement of [^{11}C]raclopride will correlate with measures of motor activity (sensori-motor striatum / Caudate / Anterior Putamen), executive function (associative striatum / dorsal caudate & posterior putamen), and Reward / Impulsivity (limbic / ventral striatum).

3. METHODS

3.1 SUBJECTS

3.1.1 Inclusion / Exclusion Criteria

Seven psychotropic medication-free adult male volunteers meeting DSM-IV criteria for ADHD were recruited by advertisement and from various ADHD clinics in Montreal, including the Adult ADHD Clinic of the Montreal Children's Hospital (Dr L Hechtman), the ADHD Clinic of the Douglas General Hospital (Dr R Joober), and the Adult ADHD Clinic of l'Hôpital Rivière des Prairies, affiliated with l'Université de Montréal (Dr P Lageix). These subjects were compared with five age-, sex- and IQ-matched healthy controls, recruited by means of newspaper advertisement. All subjects meeting entry criteria were asked to sign an informed consent form describing the procedure, prior to being enrolled in the study. Because of reported decreases in MPH and *d*-AMP-induced striatal DA release with age in healthy adults (Laruelle et al 1995; Volkow et al 1994, 2001; Leyton et al 2002), we recruited only subjects between 19 and 43 years of age.

Recently, it has been demonstrated that sensitization of the dopaminergic response to *d*-AMP, induced by just three administrations over the course of five days, is maintained for a period of at least one year (Boileau et al 2006). We therefore excluded all participants who had ever received treatment with stimulants or been exposed to stimulants in the 24 months preceding entry into the study.

Healthy Volunteers

Exclusion criteria:

Current or past personal history of Axis I psychiatric disorder

1st degree family history of ADHD, substance dependence or psychotic illness

Past or current treatment with methylphenidate, or any other medication documented to directly or indirectly modulate dopaminergic neurotransmission

Beck Depression Inventory score greater than 10; IQ<90

Cardiovascular, neurological or other disorders (including head injury) that might be aggravated by participation in the study or complicate interpretation of the study's results

A positive test on urine tox screen (cocaine, opiates, phencyclidine, barbiturates, benzodiazepines, Δ^9-tetrahydrocannabinol, amphetamines) on test day mornings

In women, seropositive pregnancy test and/or breast-feeding.

ADHD

Exclusion criteria:

Current or past history of substance dependence or claustrophobia

Current Axis I DSM-IV disorder other than mild, largely non-interfering phobias

Treatment with methylphenidate, or any other medication documented to directly or indirectly modulate dopaminergic neurotransmission, in the 24 months prior to study entry

Beck Depression Inventory score greater than 12; IQ <90

Cardiovascular, neurological or other disorders (including head injury) that might be aggravated by participation in the study or complicate interpretation of the study's results

A positive test on urine tox screen (cocaine, opiates, phencyclidine, barbiturates, benzodiazepines, Δ^9 tetrahydrocannabinol, amphetamines) on test day mornings

In women, seropositive pregnancy test and/or breast-feeding.

3.1.2 Diagnostic Procedure

Structured clinical interviews for DSM-IV Axis I diagnoses (First et al 1997) were administered in order to determine if other conditions were comorbid with ADHD or were responsible for the ADHD-type symptoms reported. The early onset continuation of ADHD symptoms from childhood through adolescence and adulthood was central in making the diagnosis of ADHD. In addition, since ADHD symptomatology is often ego syntonic to the patient, input from other informants was sought for ratings of childhood and current ADHD symptoms. Childhood ADHD symptoms were assessed via the Wender Utah Rating Scale (WURS) (Ward et al 1993) completed by the subject and an informant who knew the subject well in childhood, *e.g.*, parent, older sibling. The Conners Adult ADHD Rating Scale (CAARS) (Conners et al 1999) also has a childhood symptom section and was completed by the subject and an informant. Current

ADHD symptoms were assessed via self and other report on the CAARS Long version. This is a scale with the following symptom domains: inattention & cognitive problems, hyperactivity/restlessness, impulsivity/emotional lability, and problems with self-concept. These scales have age and sex specific norms and are thus useful in providing normative views of ADHD symptoms and associated pathology.

All subjects underwent a comprehensive physical examination, including blood analysis and EKG, in order to screen for any condition precluding participation in the study.

A well-validated IQ estimate (WAIS-Revised) based on information (general knowledge), arithmetic, picture completion, and block design was obtained for all subjects. Freedom of distractibility was also assessed with both the digit span and arithmetic tests (Wechsler 1994). Only those ADHD patients reporting marked learning difficulties were excluded.

3.1.3 Phenotyping

All subjects completed a battery of neurocognitive tasks, designed to assess hyperactivity, attention, executive functions, response inhibition, impulsivity and reward sensitivity, for the purpose of cross-examination against DAT gene polymorphism and DA release.

Cognitive testing was carried out a minimum of 24h from the time of either PET scan (to exclude possible effects of stimulant administration during the scan), using computerized and written neurocognitive tests. Each subject was seated comfortably in a quiet room with an investigator, who was present to explain and set-up the tasks. The cognitive testing session lasted approximately 90 minutes on average, with a brief break in the middle.

Go/No-Go

In the computerized Go/No-Go task (Iaboni 1995), subjects are presented with a series of two-digit numbers, half of which are "active" stimuli, requiring a mouse

button press response, while the other "passive" stimuli should not be responded to. Feedback is provided after each response (or lack of response). Correct responses result in the word "Correct" appearing on the screen, and ten cents being added to the participant's total earnings. Incorrect responses, on the other hand, result in the presentation of "Incorrect" as well as the subtraction of ten cents from the participant's earnings. The task involves four different feedback conditions. In the Reward-Punishment condition, button press responses to "right" or "active" numbers result in reward, whereas responses to "wrong" or passive numbers are punished (commission errors). In the Reward-Reward condition, responses to active numbers are rewarded, as is the withholding of responses to passive numbers. Conversely, in the Punishment-Punishment condition, participants can only lose money: failure to respond to active stimuli (omission errors), and button-press response to passive stimuli (commission errors) are both punished. Finally, in the Punishment-Reward condition, participants are penalized when they fail to respond to an active number (omission error) and rewarded when they withhold their response to a passive number. Each condition includes a pretreatment phase (twelve stimuli) such that participants are able to determine, by trial and error, which stimuli are active and which are passive.

Commission errors on the go/no-go task are a measure of disinhibition, the inability to withhold a prepotent response, and impulsive samples including boys with ADHD have been shown to commit significantly more commission errors than controls (Iaboni et al 1995).

Omission errors are indicative of deficits in sustained attention. Patients with ADHD exhibit marked CPT performance deficits (Riccio et al 2002) and deficits are aggravated by the DA receptor antagonist, haloperidol (Levy & Hobbes 1996).

Acute phenylalanine/tyrosine depletion, which has been shown to reduce resting striatal DA levels in humans (Leyton et al 2004), increases the total number of commission errors committed in the Go/No-Go during conditions where subjects

are rewarded for making correct responses (Leyton et al 2007). In a small sample of patients with ADHD, Go/No-Go performance correlated with the magnitude of MPH-induced decreases in [^{11}C]raclopride BP (Rosa-Neto et al 2002).

Stop-Signal

During the stop-signal task (Williams et al 1999), subjects respond with a left- or right-mouse button press to the on-screen presentation of an X or O, respectively (go tasks). One quarter of these stimuli are presented with a tone (stop signal) that instructs the participant to withhold his or her response (stop task). The delay between the onset of the go stimulus and the stop signal is varied with a 'tracking' algorithm, such that the participant is able to successfully inhibit a response on 50% of stop tasks. This is believed to compensate for between-subject variations in reaction time (Logan 1994). The stop-signal reaction time (SSRT) is calculated by subtracting the stop-signal delay (the interval between the presentation of the go stimulus and the onset of the stop signal which produces a 50% success rate in the completion of the stop tasks) from the go-signal reaction time. SSRT is thus indicative of the speed of the inhibition process (see Logan & Cowan 1984).

The stop-signal task took an average of twenty minutes to complete and consisted of eight blocks of 32 trials each. The stop-signal delay was initially set at 250ms, then increased by 50ms following a successful inhibition, or decreased by 50ms if the participant was not able to withhold the response.

A recent meta-analytic review of 33 studies found significant differences in SSRT in both children and adults with ADHD as compared to matched controls (Lijffijt et al 2005), and MPH has been found to improve SSRT in adults with ADHD (Aron et al 2003).

Concrete and Abstract Subject-Ordered Working Memory Tests

These tasks are computer analogs of the 12-item self-ordered pointing tasks developed by Petrides & Milner (1982). Subjects are presented with 12

consecutive arrays of the same 12 stimuli. The position of each stimulus varies between arrays, and the subject's goal is to select each stimulus only once. In the concrete subject-ordered working memory test, the stimuli are easily-recognized objects, such as a bus and a light-bulb, whereas the abstract set of stimuli consists of images which are not easily given verbal descriptors.

Administration of both tasks took less than five minutes on average, and subjects were asked to refrain from speaking aloud during completion of the tests.

Visual-Spatial working memory has been proposed as an ADHD endophenotype (Castellanos & Tannock 2002), and has been demonstrated to be sensitive to dopaminergic modulation in fronto-striatal circuits (e.g. Mattay et al 2000, 2002).

Trail-Making Test

The trail-making test (Reitan 1995) has two components. In part A, subjects are required to draw a line connecting a series of consecutive numbers (one to twenty-five) as quickly as possible; in part B, the line alternates between 12 numbers and 12 letters, in ascending order (i.e. 1, A 2, B etc.). Both components evaluate spatial scanning and visuomotor speed, and part B assesses cognitive flexibility (the ability to switch between different sets of rules: set-shift).

Performance on TMT-B correlates with striatal dopamine synthesis (Vernaleken 2006), and the majority of studies suggest that adult ADHD samples have impaired performance on this measure as compared to matched controls (Hervey et al 2004, Murphy 2002).

Tower of Hanoi

The Tower of Hanoi (TOH) is an executive control task assessing problem-solving ability and planning (Shallice 1982). Participants are presented with three equally distanced pegs of the same length. On one of these pegs are stacked, in order of decreasing size, five rings. The participant's task is to transfer this stack

to another peg, one ring at a time and without placing a larger ring on top of a smaller one.

The computerized TOH (Davis & Keller 1998) from the Colorado Assessment Tests (CATs) was used in the present study. Subjects were administered a single three-peg trial as practice, and then completed two five-ring trials consecutively. Participants were not given a time a limit, and were asked to complete the tasks in as few moves as possible.

Children and adults with ADHD have been shown to perform more poorly on the TOH than matched controls (Murphy 2002, Hervey et al 2004, Pennington 1993), and performance deficits on the TOH correlate with striatal atrophy in early Huntington's patients (Peinemann 2005)

Motor hyperactivity

An actiwatch AW-L (Mini Mitter, Bend, Oregon) was worn by each subject for a period of 48 hrs, including the neurocognitive testing session. This is a small device, worn on the non-dominant ankle, that measures movement with an internal accelerometer. Sampling was obtained every minute. Motor hyperactivity is one of the primary features of ADHD, has a well-described DA component, and, among patients, individual differences are reported to correlate with [^{11}C]raclopride BP in caudate (Jucaite et al 2005). Analysis of this data will be conducted when the project is complete; it will not be presented in what follows.

Psychopathology

The following questionnaires were administered to all study participants:

ADHD: Conners' Adult ADHD Rating Scales (Conners et al 1999), adult and child, self and observer

Mood: Beck Depression Inventory (Beck 1987)

Personality: Tridimensional Personality Questionnaire (Cloninger 1987); NEO-PI-R (Costa & McCrae 1992), Barratt Impulsivity Scale (BIS-11)

3.2 PLASMA AMPHETAMINE

Plasma concentrations of amphetamine were analyzed with electron-capture gas chromatography after extraction and derivatization of amphetamine with pentafluorobenzenesulfonyl chloride (Asghar et al 2002).

3.3 NEUROIMAGING

All subjects received two PET scans on separate days between 13:00 and 17:00 on a Siemens ECAT HR+ PET scanner (maximum resolution 4.1 x 4.1 x 4.5 mm^3, full width half maximum in center of field of view in air) with lead septa removed. Approximately 1.5h before tracer injection, a catheter was inserted into the subject's antecubital vein. Sixty minutes prior to tracer injection, an oral dose of *d*-AMP was administered double-blind and in random order (0.0 or 0.3 mg/kg). Immediately prior to tracer injection, a transmission scan was performed using ^{68}Ga for attenuation correction. Approximately 7 mCi of [^{11}C]raclopride was injected as an i.v. bolus and data acquired for 60 minutes in time frames of progressively longer duration.

High resolution (1 mm) T1-weighted magnetic resonance (MR) images were obtained for all subjects (3D fast field echo scans with 160 slices, 1 mm isotropic resolution, TR = 18 ms, TE = 10 ms, flip angle = 30°) for co-registration to the PET images. These volumes are corrected for image intensity non-uniformity (Sled *et al* 1998) and linearly and non-linearly transformed into standardized stereotaxic space (Talairach & Tournoux 1988) using automated feature-matching to the MNI305 template (Collins *et al* 1994b; Collins & Evans 1997). Each individual's MRI is then co-registered to their summed radioactivity PET images (Evans *et al* 1992). Movement correction was made for all subjects by applying an algorithm that corrects for between-frame misalignment due to head movement. This co-registration method realigns each PET frame to a ligand-specific, MRI-derived, 4 dimensional template, which represents radiotracer spatial distribution at each time point (Sechet *et al* 2002; Reilhac *et al* 2003).

PET images were reconstructed with a filtered backprojection using a 6 mm full width half maximum Hanning filter. Parametric images were then generated by calculating [^{11}C]raclopride binding potential ($BP=B_{Avail}/Kd$; B_{Avail} = density of available receptors) at each voxel using a simplified reference tissue compartmental model (SRTM) with cerebellar activity as the reference (Lammertsma & Hume 1996; Gunn *et al* 1997). A voxel-wise statistical mapping method using the SRTM model was then used to assess the t-statistic associated with the difference in [^{11}C]raclopride BP between the two scan conditions. This method applies nonlinear least squares theory on the scan's dynamic information to estimate the parameters of the kinetic model (SRTM) and utilizes the residuals to calculate associated variance (Aston et al 2000). To test for a possible relationship between voxel-wise [^{11}C]raclopride BP and relevant variables measured in every subject a regression analysis which uses voxel-wise standard deviation was applied (Worsley 1996). Clusters of statistically significant change are identified by thresholding the *t*-map at a value of $t \geq 4.2$, which corresponds to $p < 0.05$ corrected for multiple comparisons and a search volume of the entire brain volume (Worsley et al 1996).

BP values for each subject were extracted from anatomical regions of interest (ROI). Identifying the ROI entails three steps. First, each tissue type (gray matter, white matter, CSF) is automatically classified (Collins et al, 1998). Second, the striatum is delineated from a probabilistic brain atlas (Collins et al, 1994a). Third, the study's ROI is drawn within the striatum's boundaries, based on the functional organization of limbic, associative, and sensory motor sub-compartments as proposed by Laruelle, Haber and colleagues (Haber & McFarland 1999; Mawlawi et al 2001; Martinez et al 2003): ventral striatum (limbic striatum), pre-commissural dorsal caudate (posterior caudate / associative striatum), pre-commissural dorsal putamen (posterior putamen / associative striatum), post-commissural caudate (anterior caudate / associative striatum), and post-commissural putamen (anterior putamen / sensory motor putamen). The ROI are then drawn on each subject's MRI to match their individual neuroanatomy and the same regions are used for both the first and second scans. Corrections for partial

volume effects were made (Aston et al 2002). 10 consecutive 1 mm slices drawn in the cerebellum serve as the reference region. Although it has been reported that cerebellar tissue volume is reduced in ADHD patients (*e.g.*, Castellanos et al 2002), this is not expected to compromise its utility as a reference region; the required feature for this method of PET analysis is that the reference region does not have DA D2/3 receptors.

3.4 STATISTICS

3.4.1 Sample Size Estimation

A PET study by our group identified an effect of *d*-AMP (0.3 mg/kg, p.o.) on [^{11}C]raclopride binding in the ventral striatum of 10.7±9.5% (Leyton et al 2002). Power analyses indicate that a sample size of 20 subjects per group with an effect size of 1.0 will yield statistical power of 0.80 at the alpha ≤ 0.017 level of significance, an effect sufficient to survive Bonferroni corrections of our 3 primary ROI (limbic, associative, and sensory-motor sub-compartments). This seems a reasonable estimate. In previous studies, a significantly larger [^{11}C]raclopride response to *d*-AMP has been seen in patients with schizophrenia, as compared to healthy controls, with sample sizes of 11 *vs.* 12 (Breier et al 1997).

3.4.2 Data Analysis

3.4.2.1 Behavior-Cognition / Demographics

The behavioral, neurocognitive, and demographic features of each group were compared using one or two-way Group or Group x Condition ANOVAs. When appropriate, follow-up analyses were conducted with Tukey *post hoc* tests.

3.4.2.2 Amphetamine plasma levels

Plasma amphetamine levels were measured from samples drawn at 0, 60, 90 and 120 minutes post-drug (or placebo) administration. The second and final time points correspond to the beginning and end of the 60-min PET scans. Three-way, Group x Test Session x Time ANOVAs evaluated plasma amphetamine levels on the two test PET test days.

3.4.2.3 DA release

d-AMP-induced changes in [^{11}C]raclopride BP were tested in two ways. As described in Section D2, parametric mapping was conducted using the Simplified Reference Tissue Compartmental model, and *t*-maps were generated using values of $t \geq 4.2$, which corresponds to $p < 0.05$ corrected for multiple comparisons. In addition, BP values were extracted from *a priori* identified striatal ROI corresponding to the functional organization of limbic, associative, and sensory motor sub-compartments (Martinez et al 2003). A Group x ROI x Test Session x Hemisphere ANOVA was used to assess variance for *d*-AMP-induced change in [^{11}C]raclopride BP values.

3.4.2.4 Behavior / Cognition vs. DA release

Individual differences in *d*-AMP-induced change in [^{11}C]raclopride BP values were correlated with the most salient descriptors of the behavioral/cognitive phenotype, using Pearson's correlation coefficient for behavior *vs.* *d*-AMP-induced change in [^{11}C]raclopride BP in each of the ROI.

3.5 RISK AND MEASURES TO MINIMIZE RISK

Dexedrine (*d*-AMP) has a plasma half-life of 5 hours. Side effects that might occur include palpitations, mildly elevated blood pressure, restlessness, headache and dizziness. In some cases, anxiety, euphoria, or agitation may occur. Psychotic reactions are possible but at the dose that will be administered this is extraordinarily rare. No side effects, other than dry mouth, mildly elevated blood pressure and heart rate, and mild agitation were reported by any of our subjects.

Dexedrine is one of the most common treatments for ADHD, and the dose we administered is within the usual treatment range. Previous PET studies assessing DA release in patients safely administered 0.2 to 0.3 mg/kg given intravenously (*e.g.,* Laruelle et al 1996; Breier et al 1997; Abi-Dargham et al 1998). In the present study, a functionally much lower dose was given, 0.3 mg/kg, given orally, and subjects were contacted the evening of each session, and on the following

days. To date, we have administered *d*-AMP (0.3 to 0.6 mg/kg, p.o.) on over 150 occasions; serious adverse events have not occurred.

4. RESULTS

4.1 DEMOGRAPHICS, PERSONALITY, AND SYMPTOMATOLOGY

Seven male subjects meeting criteria for inclusion in the ADHD group completed all portions of the study. The neuroimaging results of two of these subjects were discarded due to excessive movement during the PET scans. The remaining five subjects were between the ages of 19 and 35 (mean ± SD, 27.20 ± 8.01 years). The age-matched control group consisted of five healthy male volunteers (mean age 29.60 ± 9.53). All subjects met inclusion and exclusion criteria, all were psychostimulant treatment-naïve, and none were current smokers. Amongst the participants with ADHD, one reported a 1st degree family history of schizophrenia, and another a 1st degree family history of depression. One control subject reported a 2nd degree family history of alcoholism. Four of the ADHD participants were of the combined DSM-IV subtype, and one was predominantly inattentive.

Personality characteristics, including scores on the BIS-11, TPQ, and CAARS-L are given in Table 1. Two-tailed t-tests revealed higher scores in the ADHD sample on the BIS-11, the Novelty Seeking measure of the TPQ, and all subscales of the self-report CAARS-L ($p<0.01$, see Table 1).

Table 1. Personality and ADHD symptoms in control and ADHD groups

		CONTROL		ADHD	
		MEAN	SD	MEAN	SD
BIS-11	**Total**	**51.0**	6.6	**86.8***	10.3
	Attentional Factor	**13.3**	1.5	**23.4***	2.8
	Motor Factor	**18.3**	3.2	**30.8***	5.6
	Non-planning Factor	**19.3**	3.1	**32.6***	4.5
TPQ	**Novelty-Seeking**	**14.8**	6.2	**24.4***	1.7
	Harm Avoidance	**6.6**	4.0	**12.2**	4.8
	Reward Dependence	**16.0**	4.7	**21.8**	4.4
CAARS-L	**Inattention/Memory**	**7.0**	3.0	**23.8***	10.0
	Hyperactivity/Restlessness	**10.4**	3.6	**26.4***	7.2
	Impulsivity/Emotional Lability	**7.2**	4.1	**18.4***	4.4
	Self-Concept	**3.6**	1.1	**11.4***	3.7
	DSM-IV Inattention	**6.3**	3.6	**18.6***	6.5
	DSM-IV Hyperactivity/Impulsivity	**5.3**	2.5	**17.8***	4.0
	DSM-IV ADHD Index	**11.5**	5.9	**36.4***	9.4
	Total Score	**8.4**	2.2	**20.8***	5.3

* Differs significantly from the mean of the control group ($p<0.01$)

4.2 NEUROCOGNITION

Separate two-way ANOVAs (Group x Condition) conducted on the TOH (conditions were Trial 1 *vs.* Trial 2), Trail-Making Test (Trails A *vs.* Trails B) and Self-Ordered Pointing Task (concrete *vs.* abstract images) yielded no main or interaction effects of group, indicating that ADHD and control subjects did not differ significantly on these measures. Commission and omission errors on the Go/No-Go were analyzed with two separate Group x Condition (Reward-Punishment, Reward-Reward, Punishment-Punishment, and Punishment-Reward) ANOVAs. No main or interaction effects of group were significant, but an unpaired one-tailed t-test indicated that ADHD subjects made significantly more commission errors during the Punishment-Punishment condition ($p<0.05$). Unpaired two-tailed t-tests conducted on the WAIS-R IQ and Stop Signal Reaction Time indicated no significant group differences on these measures.

Table 2. Neurocognitive results

			CONTROL		ADHD	
			Mean	**SD**	**Mean**	**SD**
WAIS-R IQ			**103.8**	4.26	**100.6**	3.44
Stop-Signal Reaction Time (s)			**259.2**	49.4	**261.78**	39.4
SOPT (errors)	Concrete		**1.0**	1.7	**1.20**	1.1
	Abstract		**1.2**	1.3	**2.20**	1.3
Trail-Making Test (s)	Trails A		**21.5**	3.2	**24.1**	8.6
	Trails B		**57.5**	29.3	**58.6**	16.1
Tower of Hanoi (moves)	Trial 1		**100.0**	28.6	**111.2**	91.7
	Trial 2		**80.4**	41.6	**108**	63.5
Go/No-Go (errors)	R-P	CE	**11.2**	8.2	**17.6**	16.3
		OE	**9.4**	6.6	**11.2**	3.3
	P-P	CE	**7.6**	5.3	**18.8** *	8.9
		OE	**3.6**	3.1	**1.6**	1.8
	R-R	CE	**14.2**	11.5	**17.4**	8.4
		OE	**3.4**	4.5	**5.4**	2.9
	P-R	CE	**21.2**	24.5	**18.2**	5.4
		OE	**25.0**	16.1	**24.4**	4.2
	Total	CE	**54.2**	42.0	**72.0**	25.0
		OE	**31.4**	25.2	**42.6**	4.6

*Significantly greater than control group mean (one-tailed t-test, $p<0.05$)

4.3 PLASMA AMPHETAMINE

Counter-balanced *d*-AMP administration was confirmed by measurement of plasma *d*-AMP levels at baseline and 60, 90 and 120 minutes following drug or placebo administration. *d*-AMP was not detected at baseline or during the placebo test session in any subject, though the placebo baseline sample for one control subject could not be obtained.

ADHD and control subjects did not differ significantly in plasma *d*-AMP levels: a Group x Time x Test Session ANOVA yielded no significant main or interaction effects of group (main effect of group: $p=1.23$, group x time: $p=0.08$, group x day: $p=1.23$). On *d*-AMP days, drug levels rose from 0.0ng/ml at baseline to 24.12 $\pm$ 10.15 ng/ml and 27.80 $\pm$ 9.37 ng/ml at 90 and 120 min following d-AMP administration, respectively.

4.4 SUBJECTIVE EFFECTS OF *d*-AMP

Two-way Group x Test Session ANOVAs conducted on the Visual Analog Scale change scores (peak change relative to baseline) yielded a significant main effect of session for Mind Racing ($F(1,8) = 3.98$, $p = 0.04$), which corresponded to larger increases in self-report ratings during the *d*-AMP condition. No other main or interaction effects were significant: there were no between-group differences during either the placebo or *d*-AMP conditions, and no between-session differences in either group taken separately ($p > 0.05$).

Table 3. Visual Analog Scale peak change relative to baseline.

Visual Analog Scale	CONTROL				ADHD			
	PLAC		*d*-AMP		PLAC		*d*-AMP	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Rush	0.0	1.4	1.8	3.0	-0.4	0.5	2.0	2.5
High	-0.6	1.9	2.0	3.4	-0.2	0.4	1.8	3.3
Euphoria	0.0	0.7	-0.2	1.6	0.2	0.4	1.8	3.3
Excited	0.2	1.6	1.0	3.5	-0.6	1.1	1.2	2.2
Anxious	-0.2	2.3	-1.0	1.7	0.2	1.9	0.2	1.9
Energetic	-1.4	3.2	1.2	2.9	-0.2	0.8	1.6	1.3
Like Drug	1.0	2.5	1.4	3.0	0.0	0.7	1.6	1.5
Mind Racing	0.4	1.7	2.8	3.0	-0.2	0.8	2.6	2.5
Alert	-1.2	1.9	1.0	2.3	0.6	2.5	0.4	2.9
Want Drug	-1.0	1.4	1.0	2.2	0.2	0.4	1.8	1.6

4.5 PET MEASURES

All reported binding potential values ($BP=B_{Avail}/Kd$) in the following analyses are corrected for partial volume effects (Aston et al 2002).

The Group x Test Session x ROI x Hemisphere ANOVA on [^{11}C]raclopride BP did not yield significant main effects of Group, Test Session, or Hemisphere ($p \geq 0.05$). There was, however, a significant Group x Test Session x ROI interaction ($F(4,32)=3.91$, $p=0.011$), reflecting an effect of Test Session in the ADHD group only: placebo BP was significantly greater than *d*-AMP BP in the

ventral striatum ($p < 0.02$), and nearly so in the posterior putamen ($p = 0.06$) (see Table 4 and Figure 1).

The ROI x Test Session interaction effect was also significant ($F(4,32)=6.55$, $p = 0.001$), reflecting a decrease in BP following *d*-AMP in the ventral striatum (2.53 ± 0.22 vs. 1.90 ± 0.18, $p < 0.01$) and posterior putamen (4.28 ± 0.24 vs. 3.77 ± 0.25, $p<0.05$), averaged across groups and hemispheres. BP values were lower in the ventral striatum than posterior putamen during both conditions ($p< 0.01$).

The ANOVA also yielded a main effect of ROI ($F(4,32)=27.85$, $p<0.0001$), reflecting lower BP values in the ventral striatum than in more dorsal regions ($p<0.01$), and greater BP values in posterior putamen relative to all other ROI ($p<0.01$ except posterior putamen vs. anterior putamen: $p<0.05$, see Table 3).

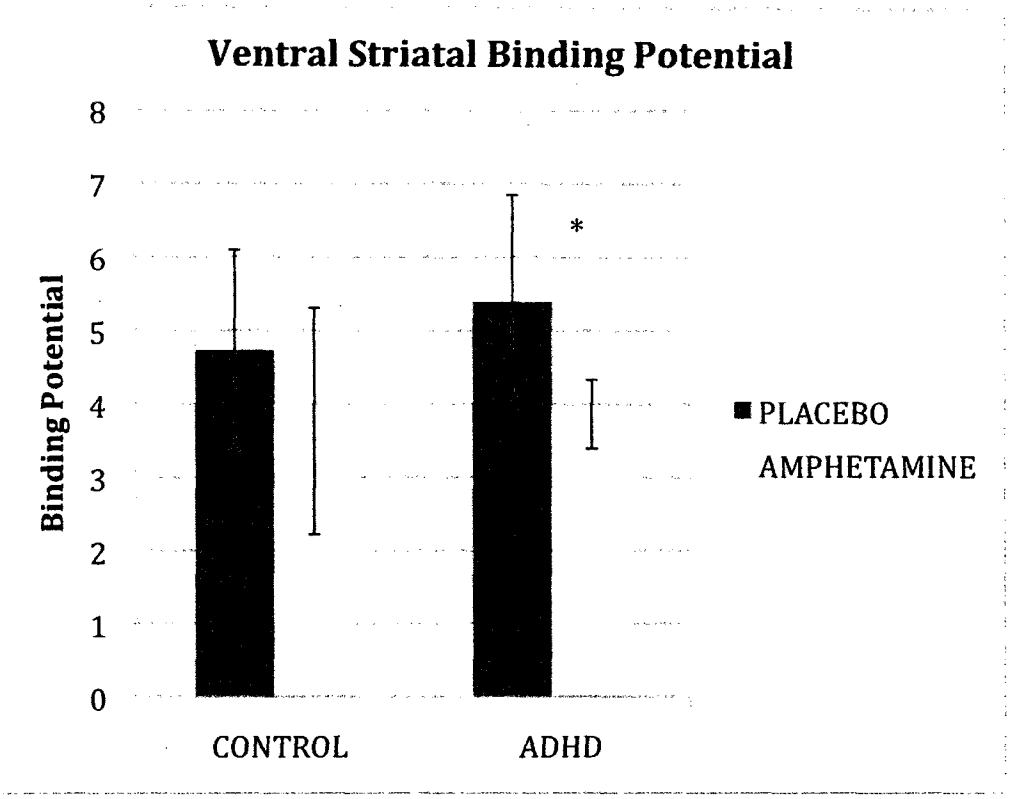
Finally, the Group x Test Session interaction effect was nonsignificant ($p > 0.05$), indicating that ADHD and control subjects did not differ in overall striatal BP following placebo or *d*-AMP administration.

Table 4. [^{11}C]raclopride binding potential (partial volume corrected) by ROI

ROI		**Control**				**ADHD**			
		PLAC		**d-AMP**		**PLAC**		**d-AMP**	
		Mean	SD	**Mean**	SD	**Mean**	SD	**Mean**	SD
Anterior Caudate	L	**2.99**	0.37	**2.80**	0.63	**3.30**	0.70	**3.30**	0.60
	R	**3.12**	0.37	**2.93**	0.55	**3.25**	0.56	**3.23**	0.44
Anterior Putamen	L	**3.27**	0.36	**3.19**	0.47	**3.66**	0.60	**3.43**	0.50
	R	**3.47**	0.27	**3.27**	0.79	**3.79**	0.75	**3.28**	0.33
Ventral Striatum	L	**2.40**	0.56	**1.91**	0.76	**2.67**	0.54	**1.89****	0.33
	R	**2.33**	0.89	**1.84**	0.78	**2.72**	0.92	**1.96****	0.23
Posterior Caudate	L	**2.66**	0.72	**2.32**	0.61	**3.34**	1.44	**3.24†**	0.87
	R	**3.24**	0.48	**2.72**	0.29	**2.88**	1.31	**3.27**	1.31
Posterior Putamen	L	**4.09**	0.40	**3.65**	0.80	**4.71**	0.96	**4.09***	0.77
	R	**3.93**	0.25	**3.47**	0.96	**4.38**	1.16	**3.87**	0.65

† greater than BP in control group ($p=0.054$), * smaller than BP in placebo condition ($p=0.051$), **smaller than BP in placebo condition ($p<0.05$). ROI = region of interest, PLAC = placebo

Figure 1. Mean (and SD) [^{11}C]raclopride binding potential in ventral striatum.



*Amphetamine BP differs significantly from placebo BP ($p<0.05$).

A Group x ROI x Hemisphere ANOVA was conducted on the *d*-AMP-induced changes in BP (%ΔBP =[BP(*d*-AMP) – BP(plac)]/BP(plac) x 100%, see Table 5). This analysis revealed a significant Group x ROI interaction effect ($F(4,32)=2.70$, $p=0.048$), corresponding to greater *d*-AMP-induced DA release in the posterior caudate in the control vs. ADHD groups ($F(1,21)=5.18$, $p=0.034$). In fact, the BP change scores among the ADHD participants were in the opposite-than-expected direction, indicating a drug-induced increase in BP in this region (ADHD: 18.06 ± 39.70% vs. controls: -12.22 ± 18.80%). The effect was most pronounced in the right posterior caudate, with all ADHD subjects demonstrating increased BP following *d*-AMP (ADHD: 21.99 ± 26.55% vs. control: -14.00 ± 18.56%, see Figures 2 & 3).

Table 5. Amphetamine-induced percentage change in [^{11}C]raclopride binding potential (%ΔBP).

		Control (%)		ADHD (%)	
		MEAN	SD	MEAN	SD
Anterior Caudate	**L**	**-10.29**	13.51	**0.72**	7.70
	R	**-5.54**	16.18	**0.56**	9.39
Anterior Putamen	**L**	**-1.54**	16.95	**-5.88**	8.18
	R	**-5.66**	21.82	**-12.22**	7.77
Ventral Striatum	**L**	**-17.59**	37.28	**-28.75**	4.35
	R	**-14.69**	37.23	**-22.41**	22.43
Posterior Caudate	**L**	**-10.45**	19.52	**14.14**	52.48
	R	**-14.00**	18.56	**21.99***	26.55
Posterior Putamen	**L**	**-10.85**	17.11	**-12.95**	3.74
	R	**-11.70**	22.73	**-9.54**	12.67

%ΔBP =[BP(*d*-AMP) – BP(plac)]/BP(plac) x 100%, negative values indicate amphetamine-induced DA release. *significantly greater than mean %ΔBP in controls (p<0.02).

Figure 2. Amphetamine-induced changes in [^{11}C]raclopride BP in right posterior caudate

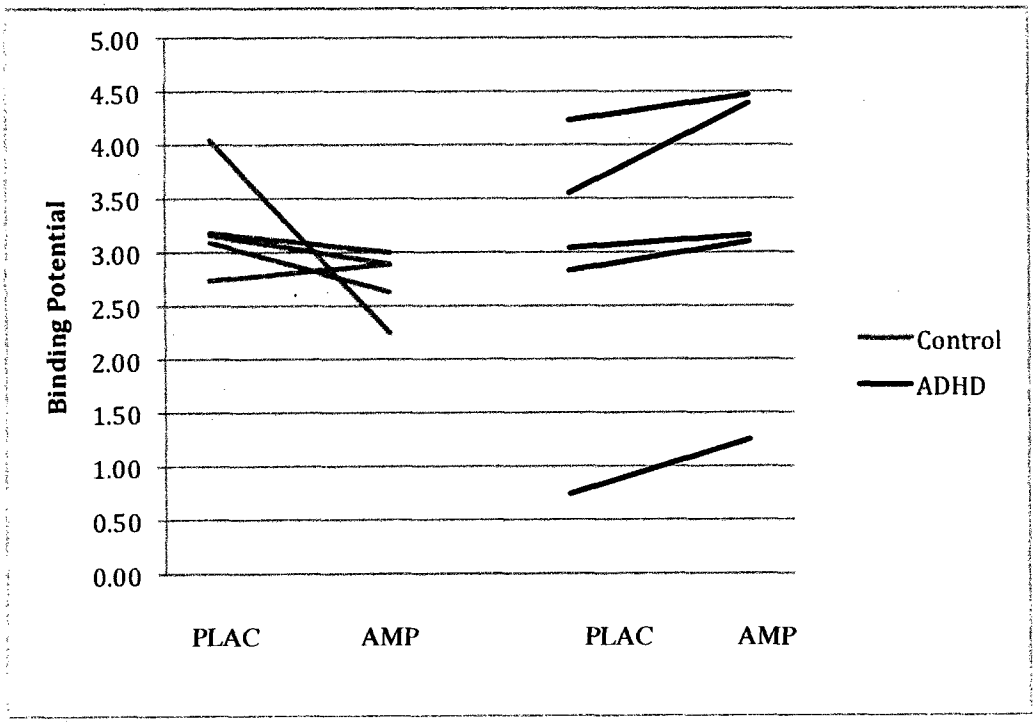
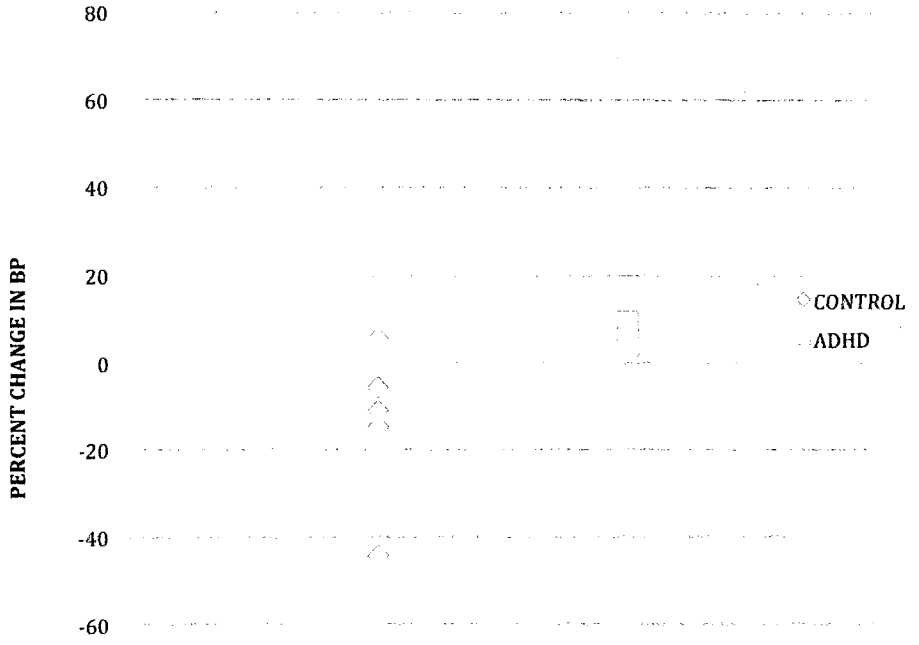


Figure 3. *d*-AMP-induced increase in right posterior caudate BP in ADHD but not control subjects.



Tukey's post-hoc tests performed on the ROI main effect ($F(9,72)=2.81$, $p=0.007$) demonstrated significantly greater BP change scores in the right ventral striatum vs. both the left ($q(72)=4.83$, $p<0.05$) and right ($q(72)=5.24$, $p<0.05$) posterior caudate in the ADHD and control groups combined.

The voxel-wise statistical mapping method revealed clusters of significant change in [^{11}C]raclopride BP following *d*-AMP in both the ADHD and control groups (Figures 4 and 5). In ADHD subjects, these clusters were observed in anterior striatum (primarily right VS, peak $t=5.01$) and posterior putamen (peak $t=7.02$). In the control group, no $t \geq 4.2$ voxels were present in the anterior striatum, but a peak $t=4.95$ was observed in the posterior putamen.

Figure 4. Group t-maps illustrating *d*-AMP-induced change in [^{11}C]raclopride BP

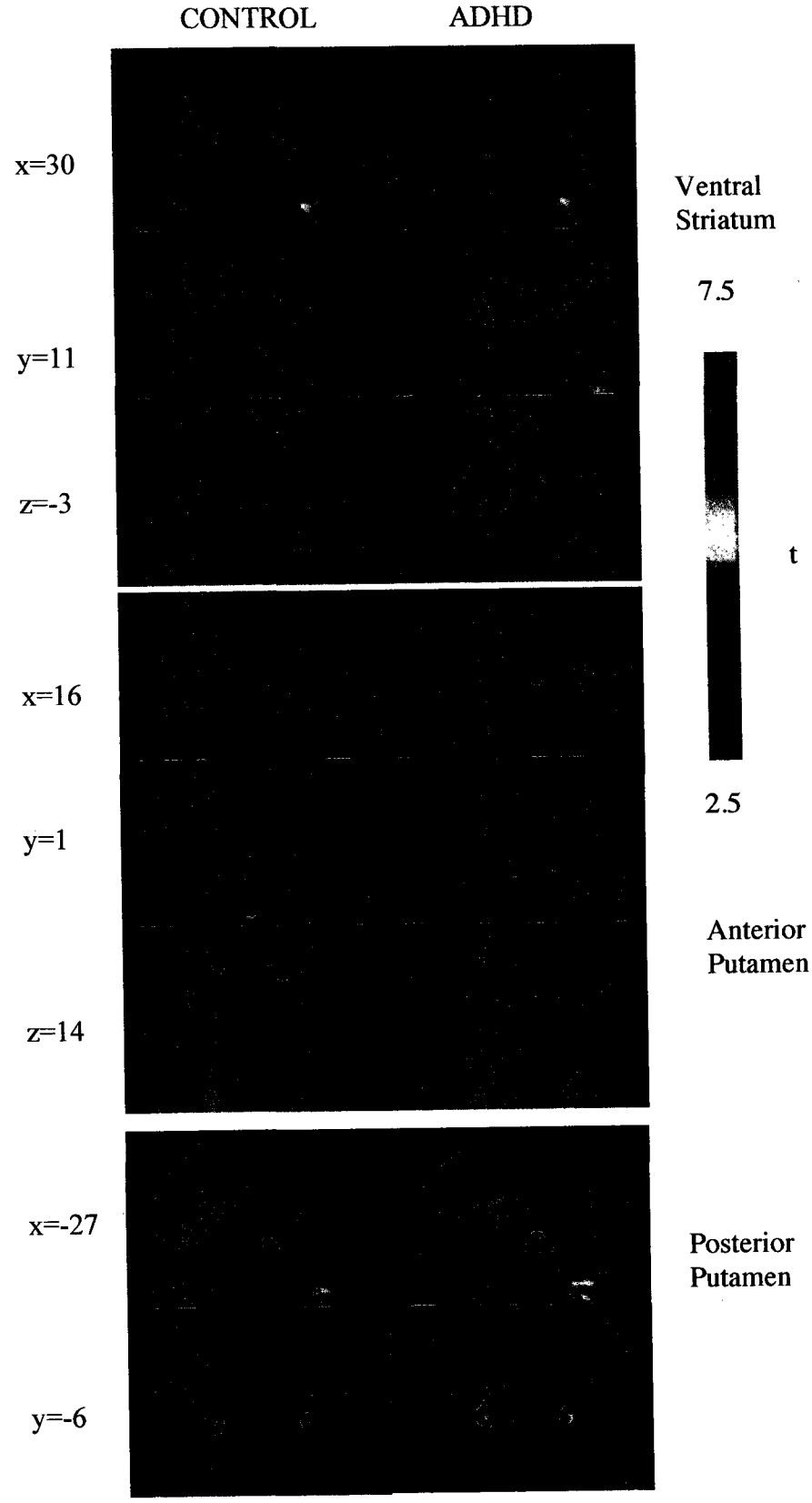
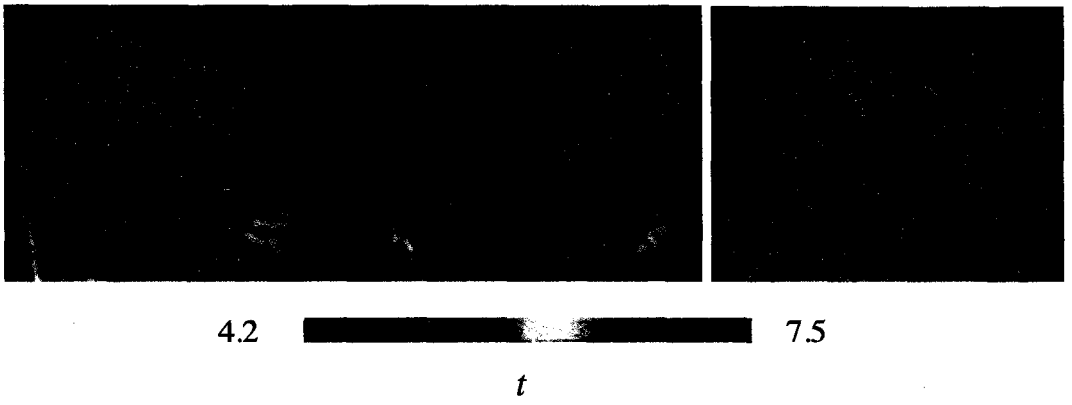


Figure 5. Averaged ADHD t-map demonstrating significant ($t \geq 4.2$) voxels of activation in the VS



4.6 CORRELATIONS BETWEEN DA RELEASE AND PERSONALITY/ NEUROCOGNITION

Pearson product moment correlations revealed no significant correlations between *d*-AMP-induced changes in BP and any of the neurocognitive or personality measures, in either of the groups or the combined sample ($p>0.05$).

5. DISCUSSION

5.1 SUBJECTS

In recent years, adult ADHD has been gaining wider recognition in both the medical community and greater public, yet it remains a sometimes contentious diagnosis. Our patients were 27.2 ± 8.0 years of age and characterized by significant ADHD symptomatology: all met criteria for a DSM-IV diagnosis (four out of five were of the combined subtype, one was inattentive) and the group as a whole demonstrated elevated scores on all subscales of the CAARS, the Novelty-Seeking measure of the TPQ, and the BIS. The comparison subjects were matched for age (29.60 ± 9.53 years) and IQ (controls: 103.8 ± 4.26 *vs.* ADHD: 100.6 ± 3.44). All participants met all inclusion/exclusion criteria, were nonsmokers, and were psychostimulant treatment-naïve.

5.2 NEUROCOGNITION

We found no significant between-group differences on any of the neurocognitive measures. This is perhaps not surprising given our small sample sizes (5 *vs.* 5) and the large inter-individual performance variability on the cognitive tasks chosen. It is worth noting that our control subjects tended to underperform relative to existing normative data. On the Stop-Signal, for example, one large study found that healthy men and women between the ages of 30 and 39 had a (mean ± SD) SSRT of (209.7 ± 63.1)s (Williams et al 1999), whereas our control group averaged (259.2 ± 49.4)s. Similarly, our healthy volunteers required a greater number of moves to complete the Tower of Hanoi than a sample of seventeen healthy subjects of a similar age (Davis & Keller 1998) (100 ±28.6 *vs.* 87.1 ± 31.4, respectively). With these considerations, the lack of a significant group effect does not rule out the presence of neurocognitive deficits in our ADHD sample. We are also unable to conclude that our control subjects were, as a whole, significantly impaired, as none had an IQ < 100, and their performance on some elements of the battery were in the expected range (e.g. Trail-Making Test; see Tombaugh 2003 for norms).

5.3 PET MEASURES

With subject groups combined, average BP values during the placebo condition were lower in the ventral striatum than in the posterior putamen, in agreement with previous PET/[^{11}C]raclopride studies in healthy subjects (Leyton et al 2002, Drevets et al 2001). Following *d*-AMP administration, BP was significantly reduced (representing DA release) in ventral striatum and posterior putamen, also as expected from published reports (*e.g.* Drevets et al 1999, Leyton et al 2002, Martinez et al 2003).

When the subject groups were separated, the *d*-AMP-induced reduction in ventral striatal BP remained significant in the ADHD subjects only; despite identical sample sizes (5 *vs.* 5), the reduction was nonsignificant in the age- and IQ-

matched comparison group. Regardless, the percent change in BP (%ΔBP =[BP(*d*-AMP) – BP(PLAC)]/BP(PLAC) x 100%) did not differ significantly between groups in this region.

In contrast, a significant between-group difference in %ΔBP was observed in posterior caudate, with particularly strong effects in the right hemisphere: BP was reduced in the control group (-14.0 ± 18.6%), yet ADHD patients demonstrated robust *d*-AMP-induced *increases* in BP (22.0 ± 26.6%). This is an unusual and unexpected finding, given the well-replicated results of *d*-AMP/[^{11}C]raclopride challenge studies and the accepted view that *d*-AMP increases intrasynaptic DA concentrations.

Though some intra-individual variability in striatal BP is expected, typical PET/[^{11}C]raclopride test-retest variability has been reported at values much too low (5.5%) to account for our results (Hietala et al 1999). Individual BP values are generally not reported in PET/[^{11}C]raclopride studies, but some studies have shown stimulant-induced increases in striatal BP of up to 30% in one or two subjects (*e.g.* Singer et al 2002). One possible explanation for our results stems from the small volume of the posterior caudate, which may be further reduced in patients with ADHD (right caudate in particular; for review see Valera et al 2007). With smaller volumes, the automated methods for motion and partial volume correction might generate inaccuracies in BP that are relatively pronounced. Further analysis with manual correction and inspection are required to determine if the stimulant-induced increase in DA release is a true effect or an artifact of the analysis methods.

If the effect holds, there are several potential explanations. As discussed above, the recent findings of one group (Mazei-Robison et al 2008) investigating a rare DAT coding variant (Ala559Val) support the possibility that in some individuals psychostimulant administration may lead to decreases in extracellular DA levels via anomalous functioning of the DA transporter. Although it is extremely

unlikely that each, if any, of our ADHD subjects possess this variant, it seems reasonable that other as-yet-unknown genetic variants could produce a similar phenotype: *i.e.*, "efflux-competent" DAT, capable of releasing DA in the baseline state, that release *less* DA when treated with amphetamine.

Another consideration in evaluating these unexpected results is that the PET technique, with its temporal resolution of 60 minutes, cannot differentiate between the two forms of cell firing described by the tonic/phasic model of DA transmission (Grace 2000). *d*-AMP has been shown to exert different effects on tonic vs. phasic DA release: while DAT blockade and reversal increase DA tone, pre-synaptic autoreceptor activation and depletion of vesicular DA stores decrease the amplitude of impulse-mediated (phasic) DA release (reviewed: Schmitz et al 2003). Thus, *d*-AMP-induced decreases in extracellular DA could result from enhanced reductions in phasic DA cell firing, relative to baseline activity, with relatively modest increases in tonic DA release[1].

At this time, two other PET/[^{11}C]raclopride studies have examined the striatal dopamine response to a psychostimulant challenge in individuals with ADHD. These studies have produced conflicting results, with one finding decreased methylphenidate-induced dopamine release in adults with ADHD relative to age-

[1] It should be noted that while some PET researchers interpret BP change as a time-averaged index of both tonic and impulse-mediated firing (*e.g.* Volkow et al 2006), others have argued that BP change primarily reflects competition at intrasynaptic D2 receptors, and is therefore more likely a measure of phasic activity. In support of the latter view, Laruelle (2000) presents the results of three studies (Kim et al 1998, Breier et al 1997, Tsukada et al 1999) evaluating microdialysate-determined extrasynaptic DA in addition to raclopride BP change following drug challenges that either block DAT directly (*e.g. d*-AMP) or enhance DA without DAT blockade (*e.g.* nicotine). Kim & Han (2009) recently expanded their original study with similar results: though methamphetamine produced an increase in extrasynaptic DA more than fifteen times that observed following nicotine (826% *vs* 51%), the drugs produced a roughly equal reduction in raclopride BP (~30%). Like Laruelle (2000), they conclude that raclopride BP changes must reflect competition at intra- rather than extrasynaptic receptors.

matched controls (Volkow et al 2007), and the other finding a correlation between symptom severity and increased DA release in adolescents with ADHD (Rosa-Neto et al 2006).

Our study differed from previous investigations on several points. First, we administered 0.3 mg/kg *d*-AMP p.o., rather than 0.3 mg/kg methylphenidate (MPH) p.o. (Rosa-Neto et al 2005), or 0.5 mg/kg MPH I.V. (Volkow et al 2007). *d*-AMP and MPH both increase extracellular DA by inhibition of DA uptake by the transporter, but their effects on DA transmission differ in several important ways: (1) *d*-AMP, but not MPH, causes the continuous, activity-independent release of DA via DAT reversal; (2) *d*-AMP has been shown to dampen impulse-mediated release of DA (by indirect actions at the D_2 autoreceptor and the depletion of vesicular stores of DA), yet MPH enhances the electrically-stimulated release of striatal DA; (3) *d*-AMP administration may have a biphasic effect on DAT expression, initially recruiting DAT to surface but soon after causing DAT internalization. MPH, on the other hand, is thought to stabilize DAT at the plasma membrane (Johnson et al 2005, Russel et al 1998, reviewed in Schmitz et al 2003). Secondly, we conducted drug and placebo scans, counter-balanced for order, on different days, while subjects in the other two studies had both scans on the same day and always in the same order. Third, our methods of analysis differed in terms of the subdivision of the striatum: both of the other groups extracted their ROI directly from the dynamic PET images, one dividing the striatal signal into putamen and caudate ROI and the other defining a single striatal volume, whereas we extracted five ROI, ventral striatum and anterior/posterior caudate and putamen, from each subject's MRI.

A model of decreased DA tone coupled with increased phasic DA activity has been proposed in ADHD patients (for review, see Sikström & Söderlund 2007). As mentioned above, given the poor temporal resolution of PET imaging, the results of the present investigation can neither support nor refute this theory. However, the finding of *d*-AMP-induced decreases in extracellular DA in

posterior caudate of our patient group may be consistent with the model. In untreated patients, chronically lowered levels of tonic DA might lead to an upregulation of D2 autoreceptors. Under normal conditions, this compensatory mechanism would not overcome the low tonic signal and phasic activity would remain relatively unchecked. Following d-AMP-induced increases in tone, however, the upregulated autoreceptors would enhance inhibition of impulse-mediated firing and an overall decease in time-averaged extracellular DA levels might thus be observed. Indeed, psychostimulants are thought to achieve their therapeutic effects through such a reduction in the relative magnitude of the phasic signal (Grace 2001, Seeman & Madras 2002). Although *d*-AMP elicited strong ventral striatal DA release in the ADHD group, these results are not necessarily contradictory, as they could point to striatal heterogeneity in autoreceptor density or other factors regulating the tonic/phasic response to the drug.

Recently, an index of glutamate levels in the anterior cingulate cortex (glutamate/glutamine-to-creatinine ratio) has been found to be decreased in adults with ADHD as compared to an age-matched control group (Perlov et al 2007). In considering the implications for striatal DA, the authors refer to a frontobasal model of DA-glutamate interaction (Carlsson et al 1999) in which prefrontal glutamate has both an activating and inhibitory affect on mesolimbic DA release, and mesolimbic DA, in turn, has a feedback effect on frontal glutamate levels. Thus, the observed reduction in cingulate glutamate in ADHD could be secondary to decreased mesolimbic DA tone or could itself be the cause of dysregulated striatal DA release (Perlov et al 2007). The possibility of reduced striatal DA tone in ADHD may be supported by findings of increased striatal DAT levels in patients (reviewed in Krause 2008, but see Volkow et al 2007). Yet, increased DAT could be an indication of increased DA terminal density and resulting enhanced DAergic transmission, rather than increased DA clearance. At this point, our understanding of DA neurotransmission and, in particular, the

biological correlates of the PET-generated BP values, is not sufficiently complete to conclusively select one or the other option.

5.4 LIMITATIONS AND FUTURE DIRECTIONS

In interpreting the results of this study, three main factors must be taken into consideration: (1) the inherent limitations of the *d*-AMP/[^{11}C]raclopride PET method, (2) the heterogeneity of the ADHD population, and (3) the small size and clinical characteristics of our ADHD sample.

Certain limitations of the PET method have been discussed. The temporal resolution of PET and binding characteristics of the raclopride ligand limit the independent characterization of both tonic and phasic aspects of DA activity, and *d*-AMP does not selectively affect one or the other form of DA release. Moreover, the PET data do not provide a direct measure of DA release itself, but instead reflect the consequences of increased extracellular DA, including competition for receptor binding, D2/D3 receptor internalization (Sun et al 2003, Ginovart et al 2004), and, potentially, other events yet to be identified. The PET/[^{11}C]raclopride method is well-validated only in the striatum, and we were thus unable to investigate DA function in other regions. Recently, our lab has validated and implemented the use of a new high affinity radioligand, [^{18}F]fallypride, to image D_2/D_3 receptor availability in both striatal and extra-striatal pathways. So far, a handful of *d*-AMP/[^{18}F]fallypride studies have been reported in humans, demonstrating expected striatal DA responses as well as significant effects in extra-striatal regions such as thalamus, amygdala, and temporal cortex (e.g. Riccardi et al 2006, Cropley et al 2008). Given the implication of frontal and limbic DA dysregulation in ADHD (*e.g.* Ernst et al 1998, Volkow et al 2007), further research making use of this ligand is warranted.

Another PET-related consideration is that ADHD and control subjects may have responded differently to the imaging procedure itself. Individuals with greater

hyperactivity and restlessness may find the hour-long imaging procedure somewhat less agreeable, and the placebo scan, as a result, may be less representative of the "baseline" state than in control subjects. However, the peak changes in VAS scores on both the placebo and drug days did not differ between groups.

In this study, the exclusion criteria for our ADHD participants (*e.g.* no comorbid conditions, no heavy smokers, limited history of drug use), while improving the homogeneity and 'purity' of our group, prevented our sample from being truly representative of the adult ADHD population (Weiss & Hechtman, 1993, Barkley, 1997a, 1997b, Mannuzza et al 1993, Faraone, 2000). However, given the heterogeneity of the disorder, a truly representative sample would be difficult to obtain. As such, future studies may compare well-phenotyped ADHD patients possessing a single additional characteristic (*e.g.* comorbid anxiety disorder) with control subjects matched for this characteristic.

6. CONCLUSION

These results provide preliminary evidence of disturbed DA neurotransmission in ADHD. In particular, we observed decreased DA levels following *d*-AMP administration in posterior caudate of adults with ADHD, an effect opposite that seen in healthy comparison subjects. Caudate DA activity is believed to be involved in several cognitive abilities critical to the successful execution of goal-directed behaviour, including working memory, set-shift, planning, and the evaluation of action-outcome contingencies (for review, see Grahn et al 2008): our results may thus be consistent with reported neurocognitive deficits in individuals with ADHD. Future studies investigating additional indices of DA function in larger patient samples are needed to characterize this DA dysregulation.

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8. APPENDIX

Please see the following pages for ethics certificates and consent forms.

Amphetamine-induced dopamine release in treatment-free adults with ADHD:
A PET/[^{11}C]raclopride study
McConnell Brain Imaging Centre
24 April 2006

CONSENT FORM

MONTREAL NEUROLOGICAL INSTITUTE & HOSPITAL
MCGILL UNIVERSITY

Departments of Psychiatry and Neurology & Neurosurgery

Title of Project: Amphetamine-induced dopamine release in treatment-naïve adults with ADHD: A PET/[^{11}C]raclopride study

Principal investigators: C Benkelfat, MD, DERBH, M Leyton, PhD

a) **Associate investigator(s) at the MNI/MNH:** A Dagher, MD.
b) **Other associate investigators (please indicate affiliations):** L Hechtman, MD (Montreal Children's Hospital), R Joober, MD, PhD (Douglas Hospital, Dept. of Psychiatry), RO. Pihl, PhD (McGill, Dept. of Psychology).
c) **Collaborators:** M Diksic, PhD (MNI); P Lageix MD (Hôpital Rivière des Prairies, U Montréal); R Lisbona MD (MNI); JP Soucy MD-MSc (MNI)
d) **Graduate students / PDF:** N Faridi, BSc (MSc candidate, McGill, Dept. of Psychiatry)

1. REASON FOR THE STUDY

Attention deficit hyperactivity disorder (ADHD) is commonly treated with stimulant medications such as Ritalin (methylphenidate) and Dexedrine (dextro-amphetamine). Both of these medications increase activity in a brain chemical system called the dopamine system. Because these medications reduce the symptoms of ADHD in most people, it is possible that there is something different about the dopamine system in people with ADHD as compared to people without ADHD.

To investigate this possibility, we plan to measure dopamine system reactivity in people with and without ADHD. The dopamine response will be elicited by administering the ADHD medication, Dexedrine (0.3 mg/kg, given orally), and measured by using a nuclear medicine procedure called positron emission tomography (PET). With this method, we will assess whether individual differences in the dopamine response are related to the symptoms of ADHD and associated. Finally, because some possible links have been found between genes that are thought to affect the dopamine system and ADHD, we plan to test whether these genes are also related to the dopamine response that we will measure.

PET is a nuclear medicine research procedure that involves the administration of small amounts (tracer dose) of a chemical that is marked (or labeled) with a radio-active particle of short or very short radioactive life; when administered intravenously to a subject, this chemical circulates in the blood to reach the brain where it will be detected by the PET camera. With the help of high power computing, researchers are then able to study the distribution of this chemical in the brain. For this study, we use a chemical called ^{11}C-raclopride (raclopride, which is labeled with the radioactive tag Carbon 11) in small amounts (tracing dose) to indirectly measure dopamine release in the human brain.

2. PROCEDURES

Your participation in this study will involve 5 sessions of about 1 to 4 hours each, probably on separate days. The first session involves a clinical interview and a medical examination. You will then have two PET sessions and a magnetic resonance imaging (MRI) session. Finally, you will be asked to complete a few computerized and oral neuropsychological tests.

A) Initial Assessment

The first session will involve an interview with one of the investigators. You will be asked to complete some paper and pencil questionnaires, and then you will meet with one of the members of the research team who will perform an interview of approximately two hours duration. The purpose of this interview is to gather background information about you and your family, and you will be asked about personal and family histories of depression, alcohol or drug problems, and other psychological disorders.

If you have ADHD, you will also be asked to complete questionnaires about the nature and severity of your symptoms. If possible, someone who knows you well (such as a parent, spouse, or co-worker) will be asked to complete similar questionnaires about you. He or she will be someone whom you've suggested. The responses you provide during the interview, as well as any other personal information obtained as a result of the study, will not be shared with your contact. If no one is available, your participation in the study will not be affected.

To ensure the absence of physical illness or problems likely to interfere with the assessment of brain function or preclude the administration of Dexedrine, you will have a physical examination and routine laboratory work, including a urine toxicology screen for drugs of abuse on the study test days. If you consent to genotyping, a nurse will draw a sample of blood.

B) Positron Emission Tomography

The PET sessions will be carried out between 11:00 and 15:00 or 13:00 and 17:00, and each scan will last about one hour. During this time, you will be asked to lie on a couch. A fine needle-catheter will be inserted into an arm vein for the administration of small amounts of the radioactive tracer, [^{11}C]raclopride, and to draw venous blood samples. On one of the PET test days, you will receive tablets of Dexedrine (0.3 mg/kg, given orally); on the other day, you will receive placebo sugar pills. The study is "double-blind", so only the lab nurse knows which pills you receive on a given day.

1) Avoid excessive fluid intake on the day of each PET scan, as you will be immobile for approximately one and a half hours during the PET scan.
2) The tracer that you will be administered is raclopride, which is labeled with the short-lived radioactive atom, carbon 11 [11-C] (physical half-life = 20 minutes). The total dose administered to you will be 13.5 millicuries, or 6.75 mCi on each PET test day.
3) During the PET study, a number of venous blood samples will be drawn from the catheter to measure levels of the tracer and amphetamine. This will be equivalent to about 40mls of blood, or 8 teaspoons per PET scan session.
4) All procedures during the PET study will be carried out by a qualified nuclear medicine technician, and supervised by a qualified nuclear medicine physician.

C) Magnetic Resonance Imaging
You will be asked to lie on a couch that will be moved into a cylindrical opening where pictures of your brain will be taken during a period of 30 to 40 minutes. The MRI machine will be quite noisy during the scan. To reduce the noise, you will be given earplugs. You will be able to communicate with the technician during the procedure. Because skin patches for transcutaneous medication administration can cause local overheating during the MRI study, you will be asked to remove any such patch before the procedure. You should bring a new patch with you if you need to re-start the medication immediately after the study.

D) Neuropsychological/Motor Activity Testing
This session will consist of several computerized and oral tests that evaluate short-term memory, ability to concentrate, and other cognitive functions that may be affected in ADHD. You will also be asked to wear a small watch-like device (Actiwatch) on the ankle of your non-dominant leg for a period of up to seven days. The Actiwatch measures movement using an internal accelerometer. This information is gathered to determine if an individual's results are correlated with his or her dopamine response to Dexedrine.

3. CONTRAINDICATION

A) For PET Study

The following are contraindications for this procedure.

1) Under 18 years old
2) Previous radiation absorbed doses received within the past 12 months that would lead, with inclusion of this study, to an aggregate total radiation absorbed dose exceeding 5 mSv (Please see Section 5).
3) Pregnancy and/or breast-feeding

B) For MRI Study

The following are contraindications for this procedure.

1) Cardiac Pacemaker
2) Aneurysm Clip
3) Heart/Vascular Clip
4) Prosthetic Valve
5) Metal Prosthesis
6) Claustrophobia

C) Dexedrine

The following are contraindications for the Dexedrine administration.

1) History of cardiovascular disease precluding the use of stimulants.
2) High Blood Pressure.
3) History of drug dependence.
4) Glaucoma.
5) Personal or family history of psychotic illness in first-degree relative
6) Pregnancy and/or breast-feeding

4. ADVANTAGES OF THE PROPOSED STUDIES

Both PET and MRI studies are tests, not treatments. It is hoped that the information obtained will help our understanding of the function of the human brain. This may, in the long term, help the diagnosis and treatment of neurological and other brain disorders.

5. DISADVANTAGES OF THE PROPOSED STUDIES

PET

1) Some discomfort may be caused by insertion of the fine needle-catheter into the vein, as well as immobility on the couch.
2) The main **RISK** of participating in this study is exposure to radiation from the short-lived tracer substance injected into your body. The administered radioactive material will expose your body to a maximal dose of 5 mSv, according to our best scientific estimates. This level of radiation dose is about twice that you receive annually from natural background radiation (0.9 - 2.2. mSv) in various regions of North America. It is also 25% of the current average annual dose limits allowed for those who work in a high radiation environment, such as nuclear medicine technicians. The degree of **RISK** associated with exposure to an additional 5 mSv of radiation is thought to be very low. This amount of additional radiation may increase the risk of fatal cancer by about 2 in 10,000 during a lifetime, while the current overall risk of fatal cancer is about 2,300 in 10,000. Similar risks, equivalent to those from the dose you are receiving, are associated with:
   (a) smoking 2 packs of cigarettes during a lifetime
   (b) driving 2,000 miles by car
   (c) flying 20,000 to 60,000 miles by air
   (d) living 100 days in New York or Boston
   Additional information available upon request

MRI

During this study, you will be exposed to a strong magnetic field. No long-term negative side effects have been observed from this type of study. As mentioned above, the MR is very noisy and you will be given earplugs to reduce this effect.

Dexedrine
Dexedrine is currently in clinical use in Canada for the management of ADHD and a sleep-disorder (narcolepsy). Side-effects of this drug include palpitations, mildly elevated blood pressure, restlessness, headache and dizziness. In some cases, anxiety, euphoria or agitation may occur. Sustained high doses of amphetamine (>100mg /day) can lead to dependence or cause psychosis, but this is very rare at the dose you will receive. The acute effects are transient and wear off after three hours. Participants will be asked to remain in the McConnell Brain Imaging Center of the Montreal Neurological Institute for observation during these three hours. If an adverse response were to develop, the participant would be treated by one of the study's physicians as deemed necessary.

6. EFFECTS OF PARTICIPATION IN THIS STUDY ON YOUR TREATMENT

Positron emission tomography, magnetic resonance imaging, the administration of Dexedrine are not expected to interfere with any treatment or other diagnostic tests.

7. CONFIDENTIAL NATURE OF THIS STUDY

The results of the testing will be kept confidential. No personal information will be released to third parties without your written approval. Your name, date of birth, address and telephone number may have to be forwarded to the Canadian Nuclear Safety Commission, upon request.

All of the genetic information obtained about you will be coded. The study file will be kept at the Research & Training Building of McGill University's Dept. of Psychiatry under the responsibility of Drs. Leyton and Benkelfat. Unless you have provided specific authorization or where the law permits or a court order has been obtained, your personal results will not be made available to third parties such as employers, governmental organizations (except for Health Canada), insurance companies or educational institutions. Blood samples will be stored for no more than ten years after the end of the research project. After this time, all samples will be destroyed unless the participant provides written consent that the samples can be kept longer. Blood samples will only be used for research protocols.

The Research Ethics Board or Quality Assurance Officers duly authorized by it may access study data.

8. INCIDENTAL FINDINGS

Research scans are not subject to clinical review. However, any incidental findings will be communicated to you and, upon your request, to your physician.

9. DISCONTINUATION OF THE STUDY BY THE INVESTIGATOR

At any time during the testing, the investigators have the right to terminate the study for any reason.

10. COMPENSATION

Upon completion of both MRI and PET studies you will receive $300 for your time and inconvenience. If studies have to be terminated for any reason, this sum will be adjusted according to the fraction of the studies completed.

IT IS ESSENTIAL FOR THE SUBJECT THAT THIS DECLARATION OF CONSENT BE FILLED OUT BY A PHYSICIAN, THE SUBJECT AS WELL AS THE INVESTIGATOR.

SUBJECT'S DECLARATION OF CONSENT

Title of Project: Amphetamine-induced dopamine release in treatment-free adults with ADHD: A PET/[^{11}C]raclopride study

Place of Testing: **Montreal Neurological Institute**

I, _____, have read the above description with

one of the above investigators, _____.

I fully understand the procedures, advantages and disadvantages of the study which have been explained to me. I freely and voluntarily consent to participate in this study.

I hereby certify that I have not participated in a PET investigation anywhere before (within the past Twelve (12) months).

Further, I understand that I may seek information about each test either before or after it is given, that I am free to withdraw from the testing at any time if I desire, and that my personal information will be kept confidential.

SIGNATURE	_____	_____	_____
	SUBJECT	***DATE***	***CONTACT NO.***
SIGNATURE	_____	_____	_____
	INVESTIGATOR	***DATE***	***CONTACT NO.***
SIGNATURE	_____	_____	_____
	PHYSICIAN	***DATE***	***CONTACT NO.***

QUESTIONNAIRE FOR MAGNETIC RESONANCE IMAGING

1. Previous surgery (type and date) _____

2. Does the subject have any of the following?	YES	NO
a) Cardiac pacemaker	____	____
b) Surgical clip on an aneurysm or other vessel	____	____
c) Surgical clip or valve on the heart	____	____
d) Prostheses (please specify type and location)	____	____
e) Implants (please specify type and location)	____	____
f) Metal or metallic fragments in any part of the body (please specify)	____	____
g) Skin patches (if you need to re-apply your patch immediately after the study, you should bring a new patch)	____	____
3. Is the subject currently taking prescription medication?	____	____

SIGNATURE	_____	_____	_____
	SUBJECT	***DATE***	***CONTACT NO.***
SIGNATURE	_____	_____	_____
	INVESTIGATOR	***DATE***	***CONTACT NO.***

Neurotransmission dopaminergique et le Trouble de Déficit de l'Attention avec Hyperactivité (TDAH)
Centre d'imagerie cérébrale McConnell
24 Avril 2006

FORMULAIRE DE CONSENTEMENT

INSTITUT ET HÔPITAL NEUROLOGIQUES DE MONTRÉAL
Centre d'imagerie cérébrale McConnell, départements de médecine nucléaire et de neuroradiologie.

Titre du Projet: Neurotransmission dopaminergique et le Trouble de Déficit de l'Attention avec Hyperactivité (TDAH)
Investigateurs principaux: M. Leyton PhD, C. Benkelfat MD, DERBH
a)Investigateurs associés à l'INM/HNM: A. Dagher MD
b)Autres investigateurs associés: L. Hechtman MD (L'Hôpital de Montréal pour enfants), R. Joober MD, PhD (Hôpital Douglas), R.O. Pihl PhD (McGill, Dépt. de Psychologie)
c)Collaborateurs : M. Diksic, PhD (INM), P Lageix MD (Hôpital Rivière des Prairies, U Montréal), R. Lisbona MD (INM), J.P. Soucy MD, MSc (INM)
d)Etudiant gradué: N. Faridi BSc (McGill, Dépt. de Psychiatrie)

1. MOTIF DE L'ETUDE

Le trouble de déficit de l'attention avec hyperactivité (TDAH) est habituellement traité avec des médicaments psychostimulants tels que le Ritalin® (methylphenidate) et la Dexedrine® (dextro-amphétamine). Ces deux traitements augmentent l'activité d'un système chimique au niveau cérébral appelé le système dopaminergique. Dans la mesure ou ces médicaments réduisent les symptômes du TDAH chez la plupart des patients traités, il est possible que le système dopaminergique des patients affectés par le TDAH soit différent de celui des personnes indemnes de cette affection.

Pour étudier cette hypothèse nous proposons de mesurer la réactivité du système dopaminergique chez des sujets avec et sans TDAH. La réponse dopaminergique sera obtenue par l'administration d'un des traitements de le TDAH, la Dexédrine® (0,3 mg/Kg administré oralement), et mesuré par l'intermédiaire d'une procédure de médecine nucléaire appelée la tomographie par émission de positons (TEP). Avec cette méthode nous évaluerons si les différences entre les réponses dopaminergiques de chaque individu sont reliées aux symptômes du TDAH. De plus, étant donné que des liens ont été suggérés entre des gènes impliqués dans le système dopaminergique et le TDAH, nous projetons d'examiner si certains de ces gènes sont également liés à la réponse dopaminergique que nous mesurerons.

La TEP est une procédure de médecine nucléaire qui comprend l'administration de petites quantités (dose traçante) d'un produit chimique lié à une particule radioactive à demie-vie courte ou très courte, communément appelée un radiotraceur. Après son injection, ce radiotraceur circule dans le sang pour atteindre le cerveau où il sera capté par la camera TEP. Ainsi, les chercheurs disposent d'un outil permettant d'étudier le comportement du radiotraceur et sa distribution dans le cerveau. La présente étude utilisera un radiotraceur appelé le ^{11}C-raclopride, administré en dose traçante pour mesurer indirectement la concentration de dopamine dans le cerveau.

2. PROCÉDURES

Votre participation à cette étude impliquera 5 sessions d'environ 1 à 4 heures chacune, probablement effectuées lors de jours séparés. La première session comporte un entretien et un examen médical. Par la suite vous aurez deux sessions de TEP et une session d'imagerie par résonance magnétique (IRM). Enfin, il vous sera demandé d'effectuer quelques tests neuropsychologiques.

A) Evaluation initiale

La première session comprendra un entretien avec l'un des membres de l'équipe de recherche. Vous serez invités à remplir quelques questionnaires, puis, le chercheur aura avec vous une entrevue d'une durée approximative de deux heures. Le but de cette entrevue est de recueillir des informations sur votre passé personnel et celui de votre famille, et nous vous poserons des questions relatives à la notion d'antécédents personnels et familiaux de dépression, de problèmes liés à la consommation d'alcool ou de drogue, et d'autres désordres psychologiques. Si vous êtes affectés par un TDAH, vous serez également invités à remplir des questionnaires concernant la nature et la sévérité de vos symptômes.

Pour s'assurer de l'absence de maladie ou de problèmes physique susceptibles d'interférer avec l'évaluation de la fonction cérébrale ou contre-indiquant l'administration de Dexedrine®, vous serez soumis à un examen physique, des analyses de laboratoire de routine, ainsi qu'une recherche de drogues dans les urines les jours d'étude.

B) Tomographie par émission de positons

Les session de scans TEP seront effectuées entre 12:30 et 17:00 heures et la durée de chaque scan sera d'environ une heure (effectué approximativement entre 14:30 et 15:30). Pendant cette période, vous devrez rester allongé(e). Une aiguille-cathéter fine sera insérée dans une veine d'un de vos bras pour l'administration d'une faible quantité de traceur radioactif, [^{11}C]raclopride et pour prélever des échantillons de sang veineux. Durant l'une des sessions de TEP, vous recevrez des comprimés de Dexedrine® (0,3 mg/kg, donnés oralement); durant l'autre session, vous recevrez des comprimés contenant un placebo (une pilule qui ne contient pas de médicament, ex. Lactose). L'étude est en "double aveugle" et seule l'infirmière de recherche connaîtra le contenu de la pilule que vous recevez un jour donné.

1) Il vous sera demandé de ne pas trop boire le jour de chaque session TEP car vous serez amené à rester immobile approximativement une heure et demie pendant le scan TEP.
2) Le traceur qui vous sera administré est du raclopride lié à une particule radioactive à demi-vie très courte, le carbone 11 [^{11}C] (demi-vie physique = 20 minutes). La dose totale qui vous sera administrée est de 13.5 millicuries, soit 6.75 mCi lors de chacun des deux scans.
3) Au cours de cette étude TEP, des prélèvements sanguins seront effectués à partir du cathéter mis en place au début de chaque session de scan TEP pour mesurer les quantités de traceurs et d'amphétamine. Le volume des prélèvements sera d'environ 40ml de sang (ou 8 cuillères à thé), lors de chaque scan.
4) Toutes les procédures effectuées au cours de cette étude TEP seront effectuées par un technicien qualifié en médecine nucléaire et supervisées par un médecin qualifié en médecine nucléaire.

C) Procédure IRM
Vous serez invité(e) à vous allonger sur la table de l'appareil que l'on fera glisser dans une ouverture cylindrique pour prendre des images de votre cerveau pendant 30 à 40 minutes. L'appareil IRM fait beaucoup de bruit durant cette opération. Pour atténuer ce bruit, nous vous donnerons des bouchons pour vos oreilles. Vous pourrez communiquer avec le technicien par microphone pendant le scan. Les patchs cutanés utilisés pour l'administration transcutanée de médicament peuvent causer une surchauffe locale de votre peau pendant l'examen IRM, vous serez donc invités à enlever ces patchs avant l'IRM. Vous devrez apporter un nouveau patch avec vous si le traitement doit être repris juste après l'examen IRM.

D) Genotypage
Une infirmière prélèvera un échantillon de sang (2 cuillères à soupes). À partir de ce sang nous extrairons le matériel génétique (également connu sous le nom d'ADN) et déterminerons les caractéristiques des gènes (genotypage) qui sont impliqués dans le système dopaminergique. De plus, nous essayerons de déterminer si les marqueurs génétiques identifiés à partir de l'échantillon de sang (génotypage) peuvent contribuer à expliquer les différences individuelles de comportement et de réponse à la Dexedrine®. Les génotypes que nous étudierons sont des variations normales et communes du matériel génétique humain.

E) Tests Neuropsychologiques et d'Activité
Les sessions consisteront en plusieurs tests oraux et sur ordinateur visant à évaluer la mémoire à court terme, les capacités de concentration, et d'autres fonctions cognitives qui peuvent être affectées dans le TDAH. Vous serez aussi invités à porter, pendant 2 jours, un petit appareil ressemblant un montre (Actiwatch) qui mesure les mouvements. Cette information est recueillie pour déterminer si les résultats d'un individu sont corrélés avec la réponse dopaminergique liée à l'administration de Dexedrine®.

3. Contre-indications

A) Etude TEP
Les critères suivants sont des contre-indications à cette procédure

1) Etre âgé(e) de moins de 18 ans.
2) Exposition à des doses radioactives dans les 12 derniers mois, incluant cette étude, de plus de 5 mSv en totale (Veuillez voir Section 5).
3) Grossesse ou allaitement

B) Etude IRM
Les critères suivants sont des contre-indications à cette procédure

1) Stimulateur cardiaque.
2) Clip d'anévrisme.
3) Clip cardiaque ou vasculaire.
4) Valve prothétique.
5) Prothèses métalliques.
6) Claustrophobie.

C) Dexedrine®
Les critères suivants sont des contre-indications à l'administration de Dexedrine®

1) Maladie cardiovasculaire empêchant l'utilisation de stimulants
2) Hypertension.
3) Antécédents de toxicomanie.
4) Glaucome
5) Antécédents personnels et/ou familiaux (famille immédiate)de troubles psychotiques.
6) Grossesse ou allaitement

4. AVANTAGES DES ÉTUDES PROPOSÉES

Il n'y a pas d'avantages directs associés à votre participation à cette étude, sauf peut-être l'infime possibilité que l'on découvre une condition qui vous était jusqu'alors méconnue et qui puisse être traitée. Les examens TEP et IRM constituent des tests et ne sont pas des traitements Nous espérons que les renseignements recueillis nous aideront à mieux comprendre le fonctionnement du cerveau humain. Cette recherche pourrait, à long terme, aider au diagnostic et au traitement des affections cérébrales.

5. INCONVÉNIENTS DES ÉTUDES PROPOSÉES

TEP

1) Il se peut que vous ressentiez un léger inconfort lié à l'introduction du petit cathéter à aiguille fine dans la veine, et à la position immobile prolongée sur le lit.

2) Le **RISQUE** principal de votre participation à cette étude est une exposition aux radiations des traceurs à demi-vie courte qui seront injectés dans votre organisme. Vous recevrez une substance radioactive à deux reprises au cours de cette étude (2 x 6.75mCi de ^{11}C-Raclopride). La substance radioactive administrée exposera votre organisme à une dose maximale de 5 mSv. Cette dose équivaut au double des radiations auxquelles vous êtes exposé(e) annuellement dans le cadre des rayonnements naturels (0,9 - 2,2 mSv) dans les diverses régions d'Amérique du Nord. Elle équivaut également à 25 % de la dose annuelle moyenne autorisée pour les personnes qui travaillent dans un milieu à fortes radiations, notamment les techniciens en médecine nucléaire. Le niveau de **RISQUE** qui se rattache à une exposition à 5 mSv supplémentaire est jugé très faible. Cette quantité de rayonnement augmente les risques de cancer d'environ 2 pour 10 000 durant votre vie, alors que le risque global de contracter un cancer fatal est d'environ 2 300 pour 10 000. Pour donner une idée de ce niveau de risque, voilà à quoi il correspond

a) fumer 2 paquets de cigarettes durant sa vie
b) parcourir 2 000 milles en voiture
c) parcourir 20 000 à 60 000 milles en avion
d) vivre 100 jours à New York ou à Boston

Renseignements supplémentaires sur demande

IRM
Pendant l'examen IRM, vous serez exposé(e) à un champ magnétique puissant. Aucun effet secondaire à long terme n'a été observé à l'issue de ce type d'étude. Comme nous l'avons indiqué ci-dessus, l'appareil est très bruyant et on vous donnera des bouchons d'oreille pour atténuer le bruit.

Dexedrine®
La Dexedrine® est couramment utilisée au canada dans le traitement du TDAH et des troubles du sommeil (narcolepsy). Les effets secondaires de ce médicament sont les suivants: des palpitations, une hausse modérée de la tension artérielle, une agitation, des céphalées et des vertiges. Dans certains cas, des sensations d'anxiété, d'euphorie ou d'agitation peuvent survenir. L'administration prolongée de doses élevées d'amphétamine (> 100mg/jour) peut être responsable de la survenue d'une dépendance ou de psychose, mais ces effets sont très rares aux doses que vous recevrez. Les effets de la Dexedrine® sont transitoires et s'estompent après trois heures. Pour cette raison, nous vous demanderons de rester au Centre d'imagerie cérébrale McConnell de l'Institut et Hôpital neurologiques de Montréal afin d'y être observé(e) pendant ces trois heures. Dans l'éventualité où une réaction adverse se produisait, le participant serait traité par un des médecins en charge, si cela s'avérait nécessaire.

6. EFFETS DE VOTRE PARTICIPATION SUR VOTRE TRAITEMENT

Les connaissances actuelles ne nous permettent pas de penser que la tomographie par émission de positons, l'IRM et/ou l'administration de Dexedrine® à la dose prescrite dans le test, puissent interfèrer de maniere significative avec autre traitement ou test diagnostique necessaire dans votre condition.

7. CARACTÈRE CONFIDENTIEL DE L'ETUDE

Les résultats de cette étude resteront confidentiels. Aucune donnée vous concernant ne sera transmise à un tiers sans votre autorisation écrite. Votre nom, date de naissance, adresse et numéro de téléphone pourront être transmis à la Commission canadienne de sûreté nucléaire, sur demande. Tous les dossiers seront également mis à la disposition de Santé Canada. Le comité d'éthique ou des officiers d'assurance qualité autorisés par ce dernier peuvent aussi accéder aux données de l'étude.

Toutes les informations génétiques obtenues vous concernant seront codées. Les dossiers de cette étude seront conservés dans le bâtiment Recherche et Entraînement du département de Psychiatrie de l'université McGill sous la responsabilité des Drs. Leyton et Benkelfat. À moins que vous n'ayez fourni une autorisation spéciale autorisant la divulgation des resultats, ou encore que la consultation des resultats ne soit autorisee en accord avec les dispositions legales en vigueur ou encore qu'une ordonnance de cour ne soit rendue autorisant la communication des resultats a qui de droit, vos résultats personnels ne seront pas disponibles pour consultation par des tiers, tel que des employeurs, des organismes gouvernementaux (excepté santé Canada), des compagnies d'assurance ou des établissements éducatifs. Les échantillons de sang seront conserves pendant une durée maximale de dix ans. Après ce temps, tous les échantillons seront détruits, à moins que le participant ne fournisse un consentement écrit attestant que ces échantillons peuvent être conservés plus longtemps. Les

FORMULAIRE DE CONSENTEMENT
INSTITUT ET HÔPITAL NEUROLOGIQUES DE MONTRÉAL
Centre d'imagerie cérébrale McConnell, départements de médecine nucléaire et de neuroradiologie.

Titre du Projet: Neurotransmission dopaminergique et le Trouble de Déficit de l'Attention avec Hyperactivité (TDAH)

Investigateurs principaux: M. Leyton PhD, C. Benkelfat MD, DERBH
a)Investigateurs associés à l'INM/HNM: A. Dagher MD
b) Autres investigateurs associés: L. Hechtman MD (L'Hôpital de Montréal pour enfants), R. Joober MD, PhD (Hôpital Douglas), R.O. Pihl PhD (McGill, Dépt. de Psychologie)
c)Collaborateurs : M. Diksic, PhD (INM), P Lageix MD (Hôpital Rivière des Prairies, U Montréal), R. Lisbona MD (INM), J.P. Soucy MD, MSc (INM)
d)Etudiant gradué: N. Faridi BSc (McGill, Dépt. de Psychiatrie)

DÉCLARATION DE CONSENTEMENT DU SUJET
IL EST ESSENTIEL POUR LE SUJET QUE CETTE DECLARATION DE CONSENTEMENT SOIT REMPLIE PAR UN MEDECIN, LE SUJET LUI-MEME AINSI QUE LE CHERCHEUR.
Déclaration de consentement du sujet
Je soussigné(e) _____ ai pris connaissance de ce qui précède en présence de l'un des chercheurs suivants, _____.

J'ai parfaitement compris les procédures, les avantages et les inconvénients de cette étude Je consens volontairement et librement à y participer.

Il est par ailleurs entendu que je peux demander des renseignements à propos de chaque examen avant ou après son déroulement, que je suis libre de me désister de ce protocole à tout moment si je le souhaite et que toute donnée me concernant restera confidentielle.

SUJET:_____DATE :_____

NO DE TÉLÉPHONE:_____SIGNATURE:_____

INVESTIGATEUR:_____DATE:_____

NO DE TÉLÉPHONE:_____SIGNATURE:_____

MÉDECIN:_____DATE:_____
NO DE TÉLÉPHONE:_____SIGNATURE:_____

QUESTIONNAIRE
Imagerie Par Résonance Magnétique (IRM)
BIC/MNI

Titre du projet : Neurotransmission dopaminergique et le Trouble de Déficit de l'Attention avec Hyperactivité (TDAH).

Il est **essentiel** pour le sujet que ce questionnaire **soit rempli** par un médecin, le **sujet** ainsi que par le **l'investigateur**

1. Chirurgies antérieures (type et date) _____

2. Le sujet porte-t-il un ou plusieurs des éléments suivants?	**OUI**	**NON**
Stimulateur cardiaque	_____	_____
Clip d'anévrisme ou clip sur un autre vaisseau	_____	_____
Clip chirurgical ou valve cardiaque	_____	_____
Prothèse (veuillez préciser le type et l'organe) _____	_____	_____
Implants (veuillez préciser le type et l'organe) _____	_____	_____
Métal ou fragments métalliques dans le corps (veuillez préciser) _____	_____	_____
Les patchs cutanés utilisés pour l'administration transcutanée de médicament. (Vous devrez apporter un nouveau patch avec vous si le traitement doit être repris juste après l'examen IRM)	_____	_____
3. Le sujet prend-il des médicaments prescrits en ce moment ?	_____	_____

SIGNATURE _____ _____ _____
sujet date no de téléphone

SIGNATURE _____ _____ _____
investigateur date no de téléphone

SIGNATURE _____ _____ _____
médecin date no de téléphone