

Neural Substrates Underlying Impulsivity

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ABSTRACT: Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder whose three main symptoms are impulsiveness, inattention, and hyperactivity. Although ADHD is an early developmental disorder, it may persist into adulthood, resulting in deficits associated with poor academic performance, frequent job changes, poor and unstable marriages, and increases in motor vehicle accidents. Of the three primary symptoms of ADHD, deficits in impulse control are the most challenging to the social network and the judicial system. While the etiology of ADHD remains unknown, recent work suggests that the central deficits in ADHD may be due to poor response inhibition that is linked to monoamine and prefrontal lobe deficiencies. In the past, preclinical studies designed to understand the lack of impulse control have generally been relegated to studies linked to aggression and drug abuse. With the use of innovative noninvasive techniques, like anatomical and functional magnetic resonance imaging, selective neurochemical and behavioral paradigms have converged with preclinical reports and lend support to the premise that monoaminergic neurotransmitter systems and the cortico-striatal circuitry are essential to impulse control. Furthermore, new emerging data on neural substrates underlying impulsivity have incorporated brain regions involved in reinforcement, reward, and decision making such as the nucleus accumbens, cerebellum, and amygdala. As noninvasive brain imaging, neurochemical, and behavioral approaches are combined, our knowledge of the neural networks underlying impulsivity will hopefully give rise to therapeutic approaches aimed at alleviating this disorder.

KEYWORDS: ADHD; impulsivity; animal models; brain regions; MRI

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder that affects a large population of children, with prevalence rates ranging from 4% to 12%.¹ ADHD is characterized by a triad of symptoms: hyperactivity, inattention, and

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impulsivity. Of this triad, impulsivity, or the failure to resist a drive or impulse that is oftentimes harmful to the self or others, can be a debilitating challenge to the care-takers and school systems alike. When left untreated, the expression of impulsivity can become a formidable burden to both the social and judicial systems, since a significant portion (approximately 60%) of ADHD children maintain this status into adolescence and even adulthood.²

Elucidating the neurophysiological basis of impulsivity has been the focus of several areas of research, because it is a central feature of numerous psychiatric disorders, including aggression, antisocial personality disorder, borderline personality disorder, obsessive compulsive disorder, and psychosis.^{3–5} Recent efforts to selectively study impulsivity from other coexisting features have been addressed using preclinical behavioral assessments of paradigms related to rapid decision making, intolerance to the delay of reward, and the tendency to prematurely terminate chains of responses.^{6–7} For example, in a preclinical study, the observation that rats exhibiting impulsivity would consistently choose smaller immediate rewards rather than larger delayed rewards⁸ provided valuable clues into the behavioral manifestations and neuroanatomical basis of impulsivity.

In the absence of focused studies on individual features of ADHD, the general hypothesis regarding the neural substrates underlying this disorder has been influenced primarily by the effectiveness of pharmacological agents such as methylphenidate and dextroamphetamine. These stimulants have been shown to modulate the activity of the dopaminergic and noradrenergic neurotransmitter systems in cortical and sub-cortical brain regions.⁹ The specific role of these neural substrates in ADHD is being expanded rapidly with the use of noninvasive magnetic resonance imaging (MRI). In fact, early reports utilizing these imaging techniques have confirmed that regions of the frontal lobe were compromised in ADHD boys compared to controls.¹⁰ In addition to frontal lobe deficits, recent reports have alluded to dysfunctions in the cerebellum,¹¹ cortico-striatal,¹² and cortico-striato–thalamo-cortical circuitries¹³ in ADHD individuals.

These observations have also been supported by data from other imaging techniques. In positron emission tomography (PET) studies, a decrease in the rate of glucose metabolism has been seen in many cortical areas, including the prefrontal cortex,¹⁴ while functional MRI (fMRI) studies clearly demonstrate that the brain regions involved in processing a task may be utilized differently in ADHD than controls.¹² Therefore, converging evidence from different methodologies support the hypothesis that dysfunction in cortico-striatal monoaminergic systems can lead to disruption in information transfer between regions critical to executive and motor functions subserving behavioral responses like attention and disinhibition.¹² However, when impulsivity is approached as a distinctive core feature of ADHD, one member of the monoaminergic system, serotonin, appears to play a primary role.^{15–16}

The Role of Serotonin in Impulsive Behavior

Serotonin [5-hydroxytryptamine (5-HT)] located within the CNS originates in the raphe nuclei of the brainstem. The CNS 5-HT system consists of two ascending and one descending pathway. According to the current classification of serotonin receptors, seven classes of 5-HT receptor types are known based on their selective

TABLE 1. Effects of serotonin drugs on impulsive behavior

Drug	Serotonin Effect	Impulsivity Effect
8-OH-DPAT	5-HT _{1A} agonist	Significantly decreased impulsivity
WAY 100 635	5-HT _{1A} antagonist	Significantly increased impulsivity
DOI	5-HT ₂ agonist	Significantly increased impulsivity
Ritanserin	5-HT ₂ antagonist	Trend of decreased impulsivity
RU 24969	5-HT _{1A/1B} agonist	Significantly increased impulsivity
MDL 72222	5-HT ₃ antagonist	No significant effect
Metergoline	5-HT antagonist (nonspecific)	No significant effect
<i>p</i> -Chloramphetamine (pCA)	Selective serotonin reuptake inhibitor (SSRI)	Weak biphasic effects Increased at high dose and decreased at low dose
Citalopram	5-HT releaser	No significant effect

SOURCE: Adapted from Evenden.⁷

pharmacological profiles. Serotonin receptors belong to the G protein-coupled receptor (GPCR) superfamily, with the exception of 5-HT₃ receptors, which function as ligand-gated ion channels. The GPCR superfamily is comprised of at least 14 distinct members, making it one of the most complex neurotransmitter systems.¹⁷

Over two decades ago, Linoilla and colleagues¹⁸ demonstrated that low levels of serotonin could lead to impulsive, violent, or self-destructive behavior in humans. The underlying assumption that CNS depletion of 5-HT resulted in increased impulsive responses was further supported by clinical data that used pharmacological challenges as a means of indirectly assessing the 5-HT system,^{19–20} along with pre-clinical studies that assessed behavioral paradigms.^{21–23} However, a recent report directly challenges the 5-HT deficit impulsivity model.²⁴ Utilizing a more direct measure of 5-HT levels in the prefrontal cortex, the data demonstrated that increases in 5-HT efflux in this region may also be responsible for lack of impulsive control.

One possible explanation for inconsistencies in the data may be the complexity of the serotonin system. In a very comprehensive preclinical study design, Evenden⁷ investigated the effects of several serotonin drugs on impulsive behavior, and found that these agents differentially affected impulsive behavior (see TABLE 1). Approach-

ing the behavioral trait of impulsivity as a composite of several factors, including the tendency to prematurely terminate a chain of responses, a paced fixed consecutive number (FCN) schedule and pharmacological interventions were used to demonstrate that stimulation of 5-HT_{1A} receptors reduces impulsivity measures, whereas stimulation of 5-HT_{1B} receptors increases impulsivity.⁷ With the advent of noninvasive techniques, the latter neuropharmacological studies are being combined with functional brain imaging to simultaneously assess anatomical and functional substrates in an effort to possibly resolve the conflicting data further.

Noninvasive Neuroimaging

Functional magnetic resonance imaging is a noninvasive procedure for studying brain activity. Functional MRI has greater spatial and temporal resolution than positron emission tomography and single-photon emission computerized tomography. It also has the advantage of being much more convenient and safe, because it does not require the production and administration of radioactive molecules to the subject. Functional MRI is a technique that relies on the oxygenation status of hemoglobin, and is therefore indirectly reflective of changes in blood flow and volume. The signal intensity changes related to alterations in blood oxygenation are referred to as blood oxygenation-level-dependent (BOLD) contrast.^{25–26} Enhanced neuronal activity is concomitant with increases in metabolism and changes in cerebral blood flow and volume to the area of activation.^{27–28} Therefore, the activation maps produced using BOLD imaging correlate with the spatial location of synaptic activity.²⁹

Although most fMRI studies utilize methods related to on-off paradigms,¹² pharmacological fMRI techniques using continuous input stimuli are becoming more common.³⁰ A primary goal of the present study design was to better understand the brain regions, temporal sequence, and maybe even the action mechanism of the chosen drug. With this in mind, the following preliminary study was performed to explore the role of a 5-HT drug known to decrease impulsivity⁷ in an animal model exhibiting this behavior.

Animal Model of ADHD

Although several animal models of ADHD have been proposed, including rats with neurotoxic brain lesions,³¹ dopamine alteration and hypertension,^{32–36} as well as mice with gene deletion,³⁷ the spontaneous hypertensive rat (SHR) model has been proposed as the most acceptable and frequently used animal model for ADHD.^{34–36,38} This animal model was used in studies focused on exploring all features of ADHD, including impulsivity. As expected, researchers demonstrated that SHR rats took longer to master an FCN schedule, and also exhibited increased levels of impulsivity when compared to controls.⁴ The successful use of this animal model of ADHD prompted the current study, which attempted to evaluate changes in brain activity accompanying a pharmacological intervention that resulted in a decrease in impulsivity.

METHODS

Experimental Procedures

Male Wistar Kyoto (WKY) and Spontaneously Hypertensive rats (SHR) weighing 200–300 grams were obtained from Charles River Laboratories (Charles River, MA). Animals were housed in pairs in Plexiglas cages (48 cm × 24 cm × 20 cm), maintained on 12:12 light:dark cycle (lights on at 9:00 h) and provided food and water *ad libitum*. All animals were acquired and cared for in accordance with the guidelines published in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publications No. 85-23, Revised 1985).

Imaging Studies

Four rats were anesthetized with medetomidine (Domitor, 0.02 mg), and implanted with an intracerebral ventricular line for drug injection. During MRI sessions, rats were first lightly sedated with ketamine HCl (Ketaset, 2.0 mg) plus medetomidine (Domitor, 0.02 mg), and secured in the MRI head and body restrainer (Insight NeuroImaging Systems, Worcester, Massachusetts). Once securely restrained, anesthesia was reversed with atipamezole (Antiseden, 0.1 mg). The animals were fully conscious within 5–10 min. Since disruption in 5-HT is thought to be involved in impulsivity, a 5-HT_{1A} agonist, 8-OH-2(di-*n*-propylamino)tetralin (8-OH-DPAT), shown to be effective in relieving impulsivity (see TABLE 1), was used to assess regions that may be significant in this disorder.

All images were acquired using a 4.7T/40-cm (Oxford Magnet Technology, Oxford, UK) horizontal magnet interfaced to a Paravision console (Bruker Medical Instruments, Massachusetts). High-resolution anatomical data sets were acquired using a fast spin echo (RARE) sequence (TR = 2.5 s; TE = 56 ms; echo train length = 8; field of view = 3 × 3 cm; data matrix = 256 × 256; slice thickness = 1.0 mm; number of slices = 18) at the end of each imaging session. Drug-induced changes in fMRI were monitored in the presence of 8-OH-DPAT (10 μL, i.c.v. injection of 2.0 mg/mL) at a concentration effective in relieving impulsivity. 8-OH DPAT was purchased from Sigma-Aldrich Inc, St. Louis, Missouri. Functional images were acquired for 20 minutes using a spin echo (RARE) sequence (TR = 2000 ms; TE = 8 ms; FOV = 3 × 3 cm; matrix = 64 × 64; slice thickness = 1.0 mm; number of slices = 18). Regions of interest (ROI) were drawn manually on the images according to a rat brain atlas and analyzed for changes in BOLD signal intensity at baseline and after drug administration. STIMULATE software was used to perform statistical comparisons of baseline periods to periods after drug administration with the Student's paired *t*-test to generate an activation map of the ROIs for each dataset.³⁹ The control and drug-activated imaging periods were defined as the average change in BOLD activity over time.

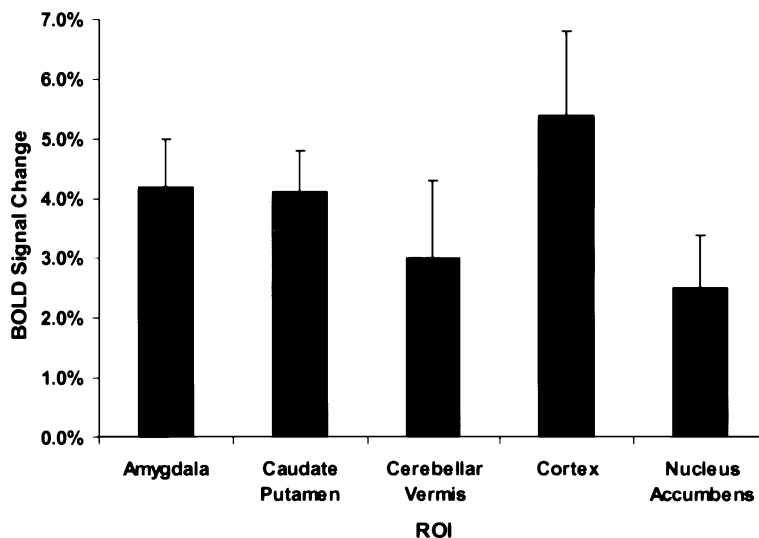


FIGURE 1. Change in BOLD signal intensity for each ROI. The BOLD signal intensity change following DPAT administration is shown for ROIs (mean \pm SEM, $N = 3$ rats). BOLD signal was averaged for each rat over the entire acquisition.

RESULTS

The data obtained from these studies are summarized in FIGURE 1. Administration of 8-OH-DPAT resulted in significant changes in BOLD signal intensity in the cortico-striatal circuitry.

FIGURE 1 depicts the average percent change (mean \pm S.E.) in positive BOLD signal intensity for the ROIs with the largest recorded signal intensities. These areas are the cortex, caudate putamen, amygdala, cerebellar vermis, and nucleus accumbens. Since all the structures analyzed are bilateral and no significant differences were found between the left and right sides, the results listed in FIGURE 1 are a combination of both hemispheres. It is also important to note that these percent-change values represent an average for the entire time series. The largest increase in BOLD signal was seen in the cortex (5.4%), followed by the amygdala (4.2%) and caudate putamen (4.1%). Finally, the cerebellar vermis and nucleus accumbens showed average BOLD signal increases of 3.0% and 2.5% above baseline, respectively.

DISCUSSION AND CONCLUSIONS

The data from this study using fMRI and 8-OH-DPAT to identify areas of brain activation associated with impulsivity corroborate the findings from clinical and pre-

clinical behavioral and fMRI studies. Since metabolic, structural, functional and behavioral studies have implicated cortical sites in ADHD,^{9,13,38,40} and specifically impulsivity,^{16,41} the changes in BOLD activity observed in the prefrontal cortex in this study occurred as expected. However, the involvement of other brain regions that are as critical to this disorder as the traditional cortical regions is becoming apparent. For example, the role of the cortico-striatal circuitry in subserving ADHD is supported by both the current observation of increases in activation in the caudate putamen, along with other reports utilizing a myriad of methodological designs.^{11,12,16} However, it is becoming clear that rather than a closed loop, the cortico-striatal circuitry is an intricate system involving other brain regions that may also be critical to the expression of impulsivity.

In the current study, three surprising regions, namely, the nucleus accumbens, amygdala, and cerebellum, experienced significant increases in BOLD activity. Although support for the participation of these sites in ADHD and impulsivity are less forthcoming, several studies lend support^{8,42-45} to a direct role for each region in the overall circuitry subserving this disorder. For example, Cardinal and colleagues⁸ investigated the role of lesions of the nucleus accumbens core on a delayed reinforcement choice task. Their report demonstrated that this lesion was selective for control of impulsive behavior, since lesions in other sites, namely the prefrontal cortex and cingulate cortex, were ineffective in modulating this behavior. The authors suggested that the nucleus accumbens was a principal site for evaluating the impact of reinforcers, a system known to be compromised in individuals with impulse control deficits. In addition, other preclinical studies utilizing the SHR animal as a model for ADHD also support the possible disruption of the nucleus accumbens in this disorder.^{44,45} Similarly, other studies in both human and animal subjects point to the involvement of additional anatomical regions, particularly the amygdala^{46,47} and cerebellum,¹¹ in the neural circuitry regulating impulsivity.

Therefore, the present preliminary study, along with data collected from many laboratories concerning the neurochemical,²⁴ neuropharmacological,⁷ and neuroanatomical¹⁶ basis of impulsivity, strongly suggests that the monoamine neurotransmitters system, specifically the serotonin system, with its abundant receptor distribution throughout the cortex, may subserve this disorder. As noted, impulsivity, or the failure to resist an impulse or drive, is a primary symptom of many disorders associated with disinhibition of behavior. Thus, the involvement of brain regions such as the nucleus accumbens and amygdala, which are linked to reward, reinforcement, and decision making, may be critical to the expression of impulsivity as a core symptom of the ADHD personality.

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