

Review

Neurobiology of ADHD

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a prevalent and debilitating disorder diagnosed on the basis of persistent and developmentally-inappropriate levels of overactivity, inattention and impulsivity. The etiology and pathophysiology of ADHD is incompletely understood. There is evidence of a genetic basis for ADHD but it is likely to involve many genes of small individual effect. Differences in the dimensions of the frontal lobes, caudate nucleus, and cerebellar vermis have been demonstrated. Neuropsychological testing has revealed a number of well documented differences between children with and without ADHD. These occur in two main domains: executive function and motivation although neither of these is specific to ADHD. In view of the recent advances in the neurobiology of reinforcement, we concentrate in this review on altered reinforcement mechanisms. Among the motivational differences, many pieces of evidence indicate that an altered response to reinforcement may play a central role in the symptoms of ADHD. In particular, sensitivity to delay of reinforcement appears to be a reliable finding. We review neurobiological mechanisms of reinforcement and discuss how these may be altered in ADHD, with particular focus on the neurotransmitter dopamine and its actions at the cellular and systems level. We describe how dopamine cell firing activity is normally associated with reinforcing events, and transfers to earlier time-points in the behavioural sequence as reinforcement becomes more predictable. We discuss how a failure of this transfer may give rise to many symptoms of ADHD, and propose that methylphenidate might act to compensate for the proposed dopamine transfer deficit.

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1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a prevalent and debilitating disorder diagnosed on the basis of persistent and developmentally-inappropriate levels of overactivity, inattention and impulsivity (American Psychiatric Association, 1994). At present there is no biomedical laboratory test for ADHD and the diagnosis is based on observation of certain behavioural symptoms. Lack of a demonstrable physical cause or causes for ADHD has led to some controversy in popular press, with media reports raising concerns about treating children with stimulant medications. However the effectiveness of drug treatment and the familial nature of the disorder have led many researchers to suspect an underlying neurobiological etiology.

The diagnostic criteria for ADHD given by DSM IV include descriptions of 9 symptoms in each of two domains (inattention and hyperactivity/impulsivity). Different subtypes are defined (Predominantly Inattentive, Predominantly Hyperactive Impulsive, Combined). Not all symptoms have to be present for the diagnosis

to be made: it is sufficient to have 6 of 9 in either domain, or both domains in the case of combined-type. Enumerating the number of ways an individual can meet criteria illustrates the potential heterogeneity of the diagnosis: the number different combinations of 6 drawn from 9 is 504.

The heterogeneous nature of ADHD as a diagnostic category has several possible implications. These criteria are used clinically and provide the grouping criteria for studies. Lack of homogeneity in study populations has led some to conclude that a single unitary cause is unlikely. The diagnosis may encompass multiple disorders each with a different etiology, in which case more homogeneous subcategories may provide refined phenotypes. Alternatively, there may be a common underlying cause that is capable of manifesting in different forms.

Our aim in this review is to address how symptoms of ADHD might arise from putative pathophysiological mechanisms. A number of reviews that have tackled the neurobiology of ADHD have focused on imaging and genetics. Relatively little attention has been given to the neurotransmitter systems involved at the cellular pathophysiology and neural systems level. In this review we focus on this middle ground, intervening between the gene and symptom level. We acknowledge that the present state of knowledge is far from complete and does not permit a complete account.

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Nevertheless, we outline a theoretical framework based on the basic neurobiology of dopaminergic actions in the frontostriatal system, which may help to integrate across these different levels of organization. We extend a previous theoretical paper, in which we proposed that altered dopamine signalling underlies a number of ADHD symptoms. We here consider how genetic alterations associated with ADHD might underlie such altered dopamine signalling, with a particular focus on dopamine receptors and transporters, and review recent evidence from combined imaging and genetic studies that address the hypothesis. We conclude by using this framework to explain some of the symptoms of ADHD and to suggest possible mechanisms for the therapeutic actions of methylphenidate.

2. Overview of etiology: genetic and brain imaging results

Genetic factors are thought play an important role in the etiology of ADHD. Family studies have consistently indicated a strong familial genetic contribution (Biederman et al., 1992, 1990; Faraone and Doyle, 2001). Twin studies have shown heritability estimates of approximately 0.8 (Kieling et al., 2008), varying between 0.6 and 0.9 (Biederman et al., 1990). It is widely acknowledged that genetic factors in ADHD are likely to involve multiple genes of moderate effect. To date no single gene has been discovered to play a major role though several gene associations have been found. The most studied are genetic variations in the dopamine D4 receptor (Swanson et al., 2000, 1998) and the dopamine transporter (DAT1) (Gill et al., 1997). Both of these have consistently been replicated (Brookes et al., 2006a) but individually they exert only weak effects and neither is necessary or sufficient for ADHD. For example, in one study DAT1 polymorphism accounted for a small fraction of the variance in symptoms in ADHD: specifically, 1.1% of variance for inattentive symptoms and 3.6% of the variance in hyperactive-impulsive symptoms (Waldman et al., 1998). A recent review of all molecular genetic studies of ADHD from 1991 to 2004 concluded there were significant associations for four genes in ADHD: the dopamine D4 and D5 receptors, and the dopamine and serotonin transporters (Bobb et al., 2006). In addition there is statistically significant evidence of association with DBH, HTR1B and SNAP-25 genes (Faraone et al., 2005), see also (Gizer et al., 2009). Genome-wide association studies have so far not reported any associations that are significant after correction for multiple testing, reviewed by Franke et al. (2009).

There is increasing recognition of potential interplay of genetic and environmental risk factors (Kieling et al., 2008; Swanson et al., 2007). Without diminishing the importance of genetic factors, environmental factors have also been identified that increase the risk for ADHD (Banerjee et al., 2007), such as exposure to lead or PCBs during early childhood, though their effects are not specific to ADHD (Williams and Ross, 2007). Recent studies suggest that causal pathways in some cases involve complex interactions between genetic and environmental factors. For example, in one study children exposed to prenatal smoking and homozygous for the DAT1 10-repeat allele were at significantly increased risk of hyperactivity, impulsivity and oppositional symptoms, while neither factor alone was associated significantly (Kahn et al., 2003). A similar interaction between prenatal alcohol exposure and the DAT1 gene has been linked to an increased risk for ADHD (Brookes et al., 2006b).

Studies of genetic association, toxin exposure, and gene by environment interactions can identify risk factors but further steps are needed to explain how the symptoms arise. Integration of such findings with additional information about the pathophysiology, and with current understanding of the neurobiology relevant to symptoms, is also required. In bridging between gene

and behaviour we need to include an understanding of how different gene variants alter the function of cells and systems of the brain.

Imaging studies have delineated gross anatomical changes in brain dimensions associated with ADHD, and a number of excellent reviews exist (Bush et al., 2005; Durston, 2003; Kieling et al., 2008; Swanson et al., 2007). The most consistent finding is an overall reduction in total brain size that persists into adolescence (Castellanos et al., 2002) and reduced dimensions of several brain regions (Hynd et al., 1993, 1990, 1991) including the caudate nucleus, prefrontal cortex white matter, corpus callosum and the cerebellar vermis. A recent meta-analysis of structural imaging findings confirms that these findings have stood the test of time, concluding that in ADHD there were regional reductions in the right caudate nucleus, the cerebellar vermis and the splenium of the corpus callosum (Valera et al., 2007). Swanson et al. (2007) in a review of the literature noted that the caudate nucleus and globus pallidus, which both contain a high density of dopamine receptors are smaller in ADHD than in control groups. Decreases in blood flow in regions of the striatum (Lou et al., 1989), and changes in dopamine transporter binding (Dougherty et al., 1999) have been described in the human striatum in ADHD. There are some inconsistencies between different studies in the association of ADHD with structural changes in the caudate and putamen, particularly those using symmetry as a measure (Krain and Castellanos, 2006). However, Tremols et al. (2008) recently reported differential abnormalities of the head and body of the caudate nucleus which may explain these inconsistencies. In the first study of the ventral striatum – the region most commonly associated with reward processing – Carmona et al. (2009) reported significant reductions in both right and left ventral striatum and a negative correlation of the volume of the right ventral striatum with maternal ratings of child hyperactivity/impulsivity.

Studies of cortical thickness have also shown changes in ADHD. A regional decrease in cortical thickness has been associated with the DRD4 7-repeat allele, which is widely associated with a diagnosis of ADHD, and with better clinical outcome (Shaw et al., 2007). This regional thinning is most apparent in childhood and largely resolves during adolescence. Diffusion tensor magnetic resonance imaging (DT-MRI) has been reported to show alterations within the frontal and cerebellar white matter in children and adolescents with ADHD (Ashtari et al., 2005).

Functional magnetic resonance imaging (fMRI) techniques are increasingly being applied to the study of brain activation in ADHD during specific cognitive and behavioural tasks. Reduced activation in prefrontal and striatal regions has been shown in a number of paradigms. Several reviews are available (Bush et al., 2005; Casey et al., 2007; Durston, 2003) covering the range of different paradigms. Here we focus on a selection of studies of particular relevance to dopamine release in the striatum, which we will need for our review of neural mechanisms. Local fMRI signals are thought to provide an indirect measure of dopamine release. In the striatum, dopamine may activate postsynaptic neurons by potentiation of corticostriatal synapses, and so increase local fMRI signals (Knutson and Gibbs, 2007). Functional activations in the striatum seem to parallel dopamine neuron activity recorded in animal studies, which will be discussed in Section 3. In particular, activation of the dorsal striatum seems to occur in relation to reinforcement of an action (Delgado et al., 2005; Haruno et al., 2004), and activation of the nucleus accumbens in relation to anticipation of reinforcement (Galvan et al., 2005). Also, imaging studies in humans have shown responses to cues predicting a juice reward in ventral and dorsal striatum. The ventral striatal area was affected by prediction error in both Pavlovian and instrumental conditioning, whereas

the dorsal striatum was affected by instrumental conditioning (O'Doherty et al., 2004, 2003). Preference for immediate over delayed reinforcement is associated with magnitude of ventral striatal activity (Hariri et al., 2006).

A recent study using fMRI in human adolescents with ADHD demonstrated reduced activation of the ventral striatum in reward anticipation relative to controls (Scheres et al., 2007). This study is important for the theory presented in the final section of this review and is presented in detail there. In a different study Plichta et al. (2009) compared brain activation in adult patients with ADHD and healthy control subjects during a series of choices between two monetary reward options that varied by delay to delivery. Reduced responsiveness of the ventral striatum to rewards was seen in ADHD patients. The significance of these changes for pathophysiological mechanisms of ADHD will be discussed in Section 5.

3. Emerging neurobehavioural concepts of ADHD

Neuropsychological studies have shown differences between children with and without ADHD on a number of tasks. Nigg (2005) undertook a meta-analysis of existing findings and identified the neuropsychological tasks that showed the greatest differences. These covered several domains and Nigg (2005) concluded that the main areas in which deficits occurred were vigilance-attention, cognitive control (sometimes referred to as executive function, and in particular reference to working memory and response suppression) and motivation (in particular, altered processing of reinforcement and incentives). Of these, two areas of functioning have been a particular focus of recent research, namely executive function, and motivational processes. These are two of the most promising or at least most studied markers. There has been sufficient interest in the executive function and motivational mechanisms for serious consideration of whether or not they have value in the diagnosis of ADHD (Sonuga-Barke et al., 2008).

At present, ADHD researchers recognise the limitations of existing diagnostic criteria in providing clues to neurobiological mechanisms. The identification of key domains of cognitive functioning is important for establishing endophenotypes that are more refined than those defined by existing diagnostic criteria (Castellanos and Tannock, 2002). Endophenotypes are bridging constructs, intermediate between underlying causes and diagnostic entities, which are specialised and represent more elementary phenomena (Gottesman and Gould, 2003; Gould and Gottesman, 2006). They define measurable components, which may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature. These basic functions are more amenable to experimental analysis in terms of neural mechanisms than behaviourally defined symptoms.

While not meeting the strict definition of endophenotypes as originally proposed in the genetic context, we illustrate the two candidates discussed here in Fig. 1. At the top level shown in the figure are symptom lists and criteria for diagnosis. These do not identify etiology, pathophysiology, or the neural systems involved. However, they have been the basis of defining study populations for research into ADHD mechanisms. At the second level we depict the two most studied cognitive endophenotypes for ADHD, which we will discuss in this section. Below that level are the brain regions showing altered structural or functional properties in ADHD, and the neurotransmitters that contribute to the cognitive functions represented by the endophenotypes. Underlying these levels are the etiological factors, such as genetic polymorphisms.

In the remainder of this section we will consider the two cognitive endophenotypes depicted in the figure.

3.1. Executive functions

Executive functions may be defined as “neurocognitive processes that maintain an appropriate problem-solving set to attain a later goal” (Willcutt et al., 2005). There is good evidence of impairment in a variety of executive function measures amongst groups of children with ADHD. However, the proposal that symptoms arise from a primary deficit in executive function is not well supported by the literature. A recent meta-analysis suggests that ADHD is associated with significant weaknesses in several key executive function domains, the most reliable being response inhibition, vigilance, working memory, and planning (Willcutt et al., 2005). However, the effect sizes were moderate and the deficits are not specific to ADHD. Executive function deficits are not specific to ADHD: they occur in children with other conditions and are not uncommon in children with no disorders (Banaschewski et al., 2005). Conversely, children can meet criteria for a diagnosis of ADHD and not show impairment of executive functions. This leads to the conclusion that ADHD is probably not specifically associated with executive function deficits (Banaschewski et al., 2005).

While there is an extensive neuroscience literature on executive function, by nature it is a higher integrative property of the fore-brain and cannot be assigned to one specific brain area, gene or neurochemical. Multiple structures may be involved in a given executive function deficit. To review the range of different functions and associated brain areas would be a major undertaking beyond the scope of this brief review. For these reasons we do not attempt to deal with the neurobiology underlying executive function deficits in ADHD, and in the remainder of this brief review we concentrate on motivation, especially in relation to delay of reinforcement.

3.2. Motivation

The second key domain of neuropsychological deficit identified in the Nigg (2005) meta-analysis was motivation, in particular in relation to reinforcement. An altered response to reinforcement has been demonstrated in children with ADHD and has been proposed as a mechanism underlying particular symptoms of ADHD by several authors (Sagvolden et al., 2005; Sonuga-Barke, 2003; Tripp and Wickens, 2008). Historically, children with ADHD have been described as less able to delay gratification and as failing to respond to discipline (Haenlein and Caul, 1987; Wender, 1971, 1972, 1974). As a group, children with ADHD have been reported to perform less well under partial reinforcement schedules (Freibergs and Douglas, 1969; Parry and Douglas, 1983), and to respond more impulsively to reinforcements; that is, to choose small immediate reinforcement over larger delayed reinforcement (Firestone and Douglas, 1975).

Luman et al. (2005) reviewed human behavioural studies published between 1986 and 2003, meeting certain methodological criteria. Differences in response to reinforcement in children with ADHD were supported by the literature. The most consistent finding is a stronger preference for immediate over delayed reinforcement. However, Luman et al. (2005) noted a lack of coherence within the existing body of literature, reflecting past lack of a common theoretical framework in which to reconcile diverse findings, and the failure of the studies to test specific predictions. Nevertheless, the literature supported the proposition that children with ADHD have an atypical response to positive reinforcement.

More recent behavioural studies of children with ADHD have extended these findings. Consistent with the conclusions of Luman et al. (2005), stronger preference for immediate reinforcers has been demonstrated in children with ADHD (Antrop et al., 2006; Hoerger and Mace, 2006). Antrop et al. (2006) showed that preference for immediacy was reduced by giving access to

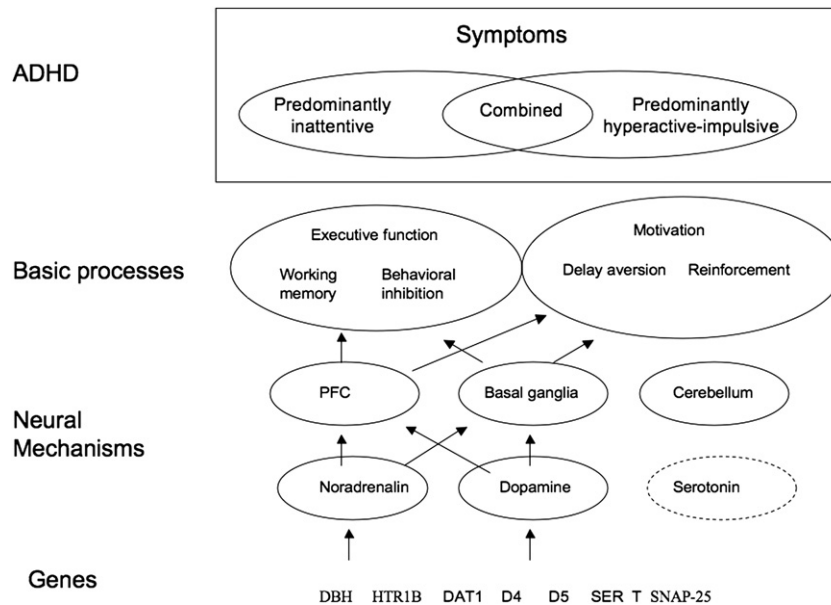


Fig. 1. Illustration of relation between levels of organization. See text for explanation.

immediate visual stimulation during the waiting period. Hoerger and Mace (2006) found that preference for immediacy correlated with measures of activity and attention in the classroom. Neef et al. (2005) found that children with ADHD were most influenced by reinforcer immediacy and quality and least influenced by rate and effort, whereas the choices of the non-ADHD group were most influenced by reinforcer quality. Aase and Sagvolden (2006) demonstrated that children with ADHD produced more variable responding under conditions of infrequent reinforcement, but not frequent, reinforcers. In contrast to these studies, Scheres et al. (2006) found no difference between children with ADHD and controls in a temporal or probabilistic reward discounting task, although they suggest possible methodological explanations for this.

Altered reinforcement mechanisms appear to be a consistent finding in children with ADHD and may be a central component of the disorder. Like executive function deficits, altered reinforcement mechanisms are not specific to ADHD and need not be present in all cases. They may, however, explain a number of ADHD symptoms. Reinforcement mechanisms in general may also involve many brain regions. However, key parts of the neural mechanism for reinforcement have a relatively well-defined neural basis. It is possible to produce specific alterations in reinforcement processes by manipulations of a single neurotransmitter system; behavioural analysis of reinforcement mechanisms has an extensive history in the context of animal learning; and it is possible to do behavioural experiments in which the effects of reinforcement are measured in humans. Because of its fundamental nature, reinforcement mechanisms can also be studied in simpler animal models which maintain relevance to humans. Therefore, the remainder of this review will focus on the neural mechanisms of reinforcement and how they may be altered in ADHD.

4. Proposed neural mechanisms underlying behavioural features

Alongside experimental studies of cognitive control and motivational processes in children with ADHD, there is an extensive literature on the neurobiology of these functions. For example, the behavioural concept of reinforcement has been extensively

researched for over a century and there have been huge advances in understanding the neural mechanisms involved in processing of reinforcement. This knowledge can be applied to understanding differences in the way children with ADHD process reward, and point to possible neurobiological underpinnings.

The neural circuits that underlie reinforcement have been studied extensively. A specific neurotransmitter – dopamine – has been strongly implicated as a mediator of the brain's reinforcement signal. The structures that have emerged as playing a central role in the reinforcement learning mechanisms are those innervated by dopaminergic projections from the midbrain. Some of these same structures have been implicated in ADHD. If ADHD involves altered reward processing, then alterations in dopamine function may underlie some of the symptoms of ADHD.

Independently of the involvement of dopamine in reinforcement, many pieces of evidence also implicate dopamine in the pathogenesis of ADHD in other ways: the most commonly used drug in the treatment of ADHD (methylphenidate/ritalin) acts on dopaminergic synapses as an indirect agonist; there is a significant association of ADHD with variants of the dopamine transporter and dopamine receptor genes; and, imaging studies showing changes in brain regions activated by dopamine. These findings provide a basis of the dopamine theory of ADHD.

4.1. Anatomy and physiology of the dopamine system

Dopamine cell bodies lie in the midbrain tegmental area where they form the pars compacta of the substantia nigra and the ventral tegmental area of Tsai in the midline (Dahlstrom and Fuxe, 1964). The terminal areas are continuous over several areas including the caudate, putamen, nucleus accumbens, amygdala, hippocampus and the cerebral cortex. Despite this anatomical continuity, medial and lateral groups are often differentiated, on the assumption that these are functionally different. Thus the substantia nigra dopamine neurons are held to largely project to the dorsolateral striatum, and to be more involved in motor control, while ventral tegmental area neurons project more ventromedially and to be more involved in cognitive or affective function (Lindvall and Bjorklund, 1974; Ungerstedt, 1971). However, physiological data on dopamine cell activity in relation to behaviour do not support this

division (reviewed by Wickens et al. (2007)). Apart from subtle differences in proportion of presumed DA cells showing reward-related activity, neuronal populations in these regions exhibit similar activity during behaviour (Ljungberg et al., 1992; Mirenowicz and Schultz, 1994, 1996; Schultz et al., 1993) suggesting that the regions of the brain receiving inputs from different DA cell groups receive a similar pattern of dopamine input.

Dopamine release is largely determined by firing activity of dopamine cells. Dopamine cells have two firing modes, a clock-like rhythmic firing mode (Grace and Onn, 1989) and firing in short bursts (Dai and Tepper, 1998; Deniau et al., 1978; Grace and Bunney, 1984a,b). In awake circumstances the regular firing pattern is hidden by synaptic inputs to the cells (Hyland et al., 2002). Dopamine cells may also show a pause in firing due to inhibitory synaptic inputs (Paladini and Tepper, 1999). In conscious animals many studies have indicated burst firing occurs in response to events connected with reward. Cells respond about 200 ms after the delivery of an unexpected reward (Mirenowicz and Schultz, 1994). Similar to the findings in non-human primates, rat dopamine cells respond to appetitive stimuli (Hyland et al., 2002), whereas aversive events inhibit dopamine cell firing (Ungless et al., 2004). Dopamine efflux in response to visual and olfactory stimuli associated with natural rewards has also been demonstrated in the rat nucleus accumbens (Ahn and Phillips, 2002, 2007; Fiorillo et al., 1997) and striatum (Nakazato, 2005). It is now widely accepted that phasic activity of dopamine cells is related to positive reinforcers.

With repeated repetition and learning of a task the dopamine burst that initially occurs at the time of the reward transfers to earlier and earlier predictors of reward (Ljungberg et al., 1992; Schultz et al., 1993). If reward is omitted in some trials, the dopamine cells are silenced at the point where an expected reward is not delivered (Mirenowicz and Schultz, 1996). These results are consistent with modern learning theory concepts of reward (Schultz, 1997, 2000; Schultz et al., 1993, 1997; Waelti et al., 2001). In particular, the reward-prediction error theory of dopamine function is that dopamine release directly encodes the difference between expected and received reward. In this theory an unexpected reward is a positive prediction error because the reward exceeds the expectation. It is signalled by an increase in dopamine release. Conversely, omission of a predicted reward produces a negative prediction error, because the reward is less than expected. Under these circumstances a decrease in dopamine release signals the negative prediction error. The human VTA has also been shown to be activated by unexpected primary rewards and displays response consistent with the reward-prediction error interpretation (D'Ardenne et al., 2008).

The neural circuitry and neurotransmitter systems that control the firing of dopamine cells are not completely understood. Dopamine cells in the ventral tegmental area and pars compacta receive glutamatergic, GABAergic, cholinergic, serotonergic and noradrenergic afferent inputs (Grillner and Mercuri, 2002). At least 70% of the inputs are GABAergic, and arise from the neostriatum, external segment of the globus pallidus, and the substantia nigra pars reticulata (Tepper and Lee, 2007). The glutamatergic inputs arise from prefrontal cortex, subthalamic, laterodorsal tegmental and pedunculopontine tegmental nuclei. The dopamine cells also receive cholinergic input from the laterodorsal tegmental and pedunculopontine tegmental nuclei. The raphe nuclei provide serotonergic, presumably inhibitory inputs, while the locus coeruleus provides an excitatory, noradrenergic input. Plasticity of glutamatergic inputs has been demonstrated and may, in part, account for transfer of the dopamine response to predictive cues (Harnett et al., 2009). Recent evidence points to crucial involvement of the lateral habenula in the control of dopamine cell firing (Hikosaka et al., 2008; Ji and Shepard, 2007; Matsumoto and

Hikosaka, 2007; Wickens, 2008). However, a great deal remains to be learnt about the circuitry and neurochemistry underlying the transfer of the dopamine signal to predictive cues.

4.2. The dopamine transporter in dopamine signalling

Dopamine uptake, release and diffusion have been the subject of several recent reviews (Arbuthnott and Wickens, 2007; Garris and Wightman, 1995; Gonon et al., 2000; Wickens and Arbuthnott, 2005). There is growing evidence for free diffusion of dopamine from the synaptic cleft and into the surrounding extracellular tissue, a form of synaptic signalling that in other systems has been called volume transmission (Agnati et al., 1995). The dopamine transporter (DAT) is responsible for terminating the dopamine signal.

As noted in Section 1, a variation of the DAT1 gene has been associated with ADHD. At the molecular level, the DAT1 gene varies in length due to a variable number tandem repeat (VNTR) polymorphism of a 40-base pair repeat unit. The number of copies in the repeat region varies and alleles with ten copies (10R) have been associated with ADHD. The VNTR occurs at a non-coding site and is thought not to affect properties of the transporter *per se* but rather its expression. When expressed in cultured cells DAT binding site density for the 10R polymorphism was elevated approximately 50% over that of the 9R allele (VanNess et al., 2005). However, depending on other conditions, both increases and decreases in DAT expression levels can be found experimentally when comparing different alleles (Miller and Madras, 2002). This may explain variations in the direction of changed DAT binding in humans with ADHD (Cook et al., 1995; Madras et al., 2005; Swanson et al., 2000; VanNess et al., 2005) although other factors may also modulate the level of DAT expression. Nevertheless, the DAT is the primary determinant of dopamine clearance after its release, and altered expression of DAT would dramatically alter the time-course and amplitude of the dopamine signal at its receptors.

Altered dopamine signalling resulting from dopamine-related genetic polymorphisms, may determine individual differences in reward sensitivity. In a recent study combining genetic approaches with imaging, the 9R allele was associated with relatively greater ventral striatum reactivity as measured by fMRI (Forbes et al., 2009). The DAT 9R allele and also the D4 7R allele were associated with impulsivity as measured by the Barratt Impulsiveness Scale which assesses tendencies to act without thinking, make decisions on the spur of the moment, and to fail to plan ahead. These findings support the hypothesis that changes in DAT expression that alter dopamine signalling may change postsynaptic responsiveness of striatal neurons. However, it should be noted that the 10R allele is the one usually associated with ADHD.

4.3. Cellular actions of dopamine

The physiological effects of dopamine transmission in the brain are mediated by a family of G-protein coupled receptors. Keibadian and Calne (1979) proposed two classes of dopamine receptor, D1 and D2, based on cAMP assays and ligand binding. These have different biochemical and pharmacological properties and physiological functions. Selective agonists and antagonists exist for each of the two subtypes. Different G-proteins and effectors are involved in the signalling pathways of D1 and D2 subtypes.

Five distinct dopamine receptors have been identified by molecular cloning techniques. These have been grouped into D1-like (D1 and D5) and D2-like (D2,3 and 4) receptors on the basis of their pharmacological profiles and sequence (Sibley and Monsma, 1992). These receptors have different regional and cellular distributions and functional properties, and several reviews exist

(de Almeida et al., 2008; Nicola et al., 2000; Wickens and Arbuthnott, 2005). The dopamine D1 and D2 receptors are more-or-less uniformly expressed throughout the striatum (caudate, putamen and nucleus accumbens) at high levels and at lower levels in cortical areas (prefrontal cortex). In the striatum the cellular expression of D1 and D2 receptors is segregated between direct (striatonigral) and indirect (striopallidal) pathways.

As noted above, polymorphisms of the D4 and D5 receptors have been associated with ADHD, so these are considered in more detail here. Unlike the other D2-like receptors, the dopamine D4 subtype is expressed at very low levels in the striatum but moderate levels in the prefrontal cortex (Meador-Woodruff et al., 1996), where it is found in both interneurons and pyramidal neurons (Ariano et al., 1997; Noain et al., 2006). In the striatum the D4 receptor is expressed presynaptically, in the terminals of the corticostriatal afferents (Berger et al., 2001; Murray et al., 1995) and not in the intrinsic neurons as the other D1 and D2-like receptors. The function of the D4 receptor is unclear at present, because selective agonists have only recently appeared. It has been associated with rapid translocation of Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) from cytosol to postsynaptic sites in cultured PFC neurons (Gu et al., 2006), an event that is important in activity-dependent plasticity of glutamate receptors. The D4 receptor also modulates a potassium conductance (the inwardly rectifying potassium current) (Pillai et al., 1998) and may modulate excitability of prefrontal neurons. Its preferential localization in the prefrontal cortex suggests a possible involvement in working memory processes, where D4 receptors may modulate the sustained increases in firing rate in relation to the mnemonic trace of a preceding event (Goldman-Rakic, 1999).

The dopaminergic innervation of the prefrontal cortex, although higher than other cortical areas, is remarkably sparse compared to the innervation of the striatum, and the density of the nerve terminals is 100-fold less (Descarries et al., 1987; Doucet et al., 1986). Both dopamine and noradrenaline have a high affinity for the D4 receptor. Moreover, there are mismatches between the location of D4 receptors and dopamine terminals, indicating that these receptors may be activated at least in part by dopamine and noradrenaline operating as volume transmission signals (Rivera et al., 2008). These factors indicate that the dopamine signals would operate on a much slower timescale than the dopamine signals of the striatum. In this respect the wave of DA increase in the prefrontal cortex is more of a slow wave compared to a spike in the striatum, suggesting it may play a different sort of modulatory role in the two areas: slowly modulating prefrontal cortical activity, but reinforcing brief activity patterns in the striatum.

Dopamine D5 receptors are expressed in cortex, hippocampus and striatum. These receptors are coupled to adenylate cyclase and activation results in increase in intracellular cyclic AMP levels, an important second messenger involved in synaptic plasticity. They are most highly expressed in striatum where they have been associated with reward-related learning (Beninger and Miller, 1998) and dopamine modulation of long-term potentiation of the synapses connecting the cerebral cortex to the striatum (Kerr and Wickens, 2001; Reynolds et al., 2001).

As well as signaling reinforcing events, animal studies have repeatedly shown that dopamine release (brought about by reinforcement-related activity of dopamine cells) is critical for learning on the basis of positive reinforcement (Beninger and Freedman, 1982; Beninger and Miller, 1998). Many pieces of evidence suggest that the mechanism that underlies this learning involves synaptic plasticity that leads to strengthening of specific synapses. This mechanism was described as a “three factor rule” for synaptic modification (Wickens, 1990, 1993). The mechanism requires presynaptic activity in cortical inputs to the striatum, postsynaptic

striatal cell activity, and phasic release of dopamine. This form of dopamine-dependent potentiation has been demonstrated at the synaptic level (Wickens et al., 1996) and is associated with behavioural learning (Reynolds et al., 2001). Consistent with this, phasic firing of dopamine cells has been shown to be sufficient for behavioural reinforcement (Tsai et al., 2009).

The convergence of evidence concerning the dopamine system, reinforcement mechanisms, and ADHD presents a remarkable opportunity for application of understanding of neurobiological mechanisms of reinforcement to the problem of altered reinforcement sensitivity in ADHD. We devote the remainder of this review to such a synthesis.

5. Synthesis of neurobiological and behavioural aspects of ADHD

We have previously proposed a theory to account for altered reinforcement processing in ADHD, which we termed dopamine transfer deficit (DTD) theory (Tripp and Wickens, 2008). This theory proposes that some of the symptoms of ADHD may be explained by a failure of the dopamine cell response to transfer to earlier predictors of reward. The theory makes the following assumptions:

- (1) In normal children, the dopamine cell response to positive reinforcement transfers to earlier cues that predict reinforcement.
- (2) This transfer provides immediate reinforcement at the cellular level when behavioural reinforcement is delayed.
- (3) In children with ADHD, the transfer of the dopamine cell response to the cue that predicts reinforcement fails to occur.
- (4) This dopamine transfer deficit leads to delayed reinforcement at the cellular level if behavioural reinforcement is delayed.

These postulates are illustrated in Fig. 2. For children with ADHD, the DTD assumes that the phasic dopamine cell response to the cue that predicts reinforcement is reduced in amplitude to the point of being ineffective, and the phasic dopamine cell response only occurs after the positive reinforcer is delivered (Tripp and Wickens, 2008; Wickens and Tripp, 1998). Thus, children with ADHD would experience a delayed dopamine signal at the cellular level, rather than the immediate anticipatory dopamine signal that normal children experience. This would explain abnormal sensitivity to delay of reinforcement.

At present we cannot account for how such a deficit arises. The neural mechanism that underlies such a transfer is not known. It is not obvious that such a deficit would arise from altered DAT1 or DRD4 function, though it is likely that changes in these would increase the effect of such a deficit. Altered prefrontal cortex function may contribute to such a deficit, but there other possibilities as well, and existing evidence does not permit a strong conclusion about the cause of the deficit.

Tasks involving a delay of reward involve other cognitive functions concerned with the perception and judgement of time. It is possible that some aspects of DTD may be explained by an inability to predict the timing of reward. While this would not be expected to impair the development of a dopaminergic response to cues associated with rewards, it might impair the ability to suppress the firing of dopamine cells at the time the actual reward was delivered. This would result in the continued presence of a dopamine response to the established reinforcer. Perception of time is a fundamental but complex cognitive function. A variety of methods have been used to measure timing performance in children with ADHD. A recent review of this topic (Toplak et al., 2006) concluded that growing evidence links ADHD to problems in

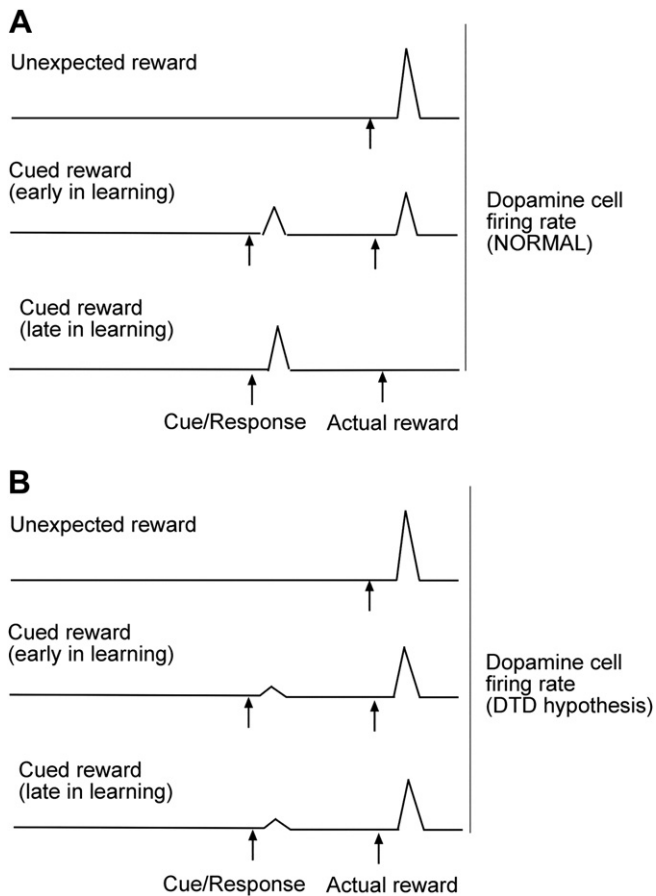


Fig. 2. Transfer of dopamine cell signalling to predictive cues and behaviours. A. Normal transfer of dopamine cell firing. Unexpected reward is a potent stimulus for dopamine cell firing activity. Early in learning, dopamine cell firing responses transfer to cues that predict later reinforcers. They may also transfer to responses, which can act as cues that predict reinforcers. Later in learning responses to cues may dominate over responses to actual reinforcers. B. Dopamine cell firing in DTD hypothesis. There is a failure of the dopamine cell firing to transfer to earlier cues that predict positive reinforcers.

several aspects of temporal information processing, including duration discrimination, duration reproduction, and finger tapping. However, because of difference in methodologies and results between studies, further replication is needed before firm conclusions can be drawn.

Although the mechanism is unclear, the assumptions of DTD are supported by studies using fMRI. Scheres et al. (2007) showed there was reduced activation of the ventral striatum in reward anticipation among adolescents with ADHD, relative to controls. In this study, participants were presented with a cue that signaled the opportunity to win money, or avoid losing money, by responding with a button press. In control trials a button press was also required, but the cues signaled no money would be won or lost. Control participants showed activation of the ventral striatum in the period after cues that signaled gain, indicating anticipatory dopamine release. In participants with ADHD, there was no significant anticipatory activation of striatal regions after cues that signaled gain. On the other hand their neural responses to the outcome were not significantly different from control participants. These findings are consistent with selective impairment in anticipatory dopamine cell firing due to a dopamine transfer deficit.

Also consistent with such impairment, Plichta et al. (2009) found reduced responsiveness of the ventral striatum to rewards in

ADHD patients compared to healthy control subjects, in a task that involved a series of choices between two monetary reward options that varied by delay to delivery. In this task it was not possible to differentiate immediate from delayed reward responses, because there was a delay on the “immediate” condition. In a study of adults with ADHD, using a monetary incentive delay task, there was decreased activation in the ventral striatum during the anticipation of gain (Strohle et al., 2008). These findings are also consistent with impairment in anticipatory dopamine cell firing. Although the mechanism of DTD is not known, it is possible to use DTD to explain several symptoms of ADHD. We have given a detailed account of this in our earlier theoretical review (Tripp and Wickens, 2008). Here we summarise the main arguments.

A number of the DSM IV symptoms of *inattention* may be due to failure of anticipatory dopamine cell firing, leading to control of behaviour by actual instances of reinforcement rather than predicted reinforcement. These symptoms include: “often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities”; “often has difficulty sustaining attention in tasks or play activities” and “is often easily distracted by extraneous stimuli”. These symptoms of “inattention” can be interpreted as off-task behaviours. In normal children, on-task behaviour (“attending”) is maintained by continuous reinforcement of attending by anticipatory dopamine release. This anticipatory dopamine release develops in normal children because their dopamine system is able to use previous instances of reinforcement to produce anticipatory dopamine release.

Other DSM IV symptoms of inattention for which the DTD theory is relevant include, “often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace”, and “often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort”. These symptoms can be interpreted as failure of conditioned reinforcers leading to increased sensitivity to delay of reinforcement and less effective performance under partial reinforcement schedules.

In contrast, the DTD theory has less explanatory power for the remaining DSM IV symptoms of inattention, namely “often does not seem to listen when spoken to directly”, “often has difficulty organizing tasks and activities”, “often loses things necessary for tasks or activities” and “often forgetful in daily activities”. These symptoms appear to involve other primary psychological processes such as internal representation of contingencies, which may not be dopamine-dependent, although the output of these processes may indirectly involve reinforcement mechanisms.

The DTD theory also explains some DSM IV symptoms of *hyperactivity* and *impulsivity*. The symptom of “often leaves seat in classroom or in other situations in which remaining seated is expected” may be interpreted as a lack of effective reinforcement for remaining seated, due to smaller activity of dopamine neurons, because of a deficit in anticipation of reinforcement. The symptoms of “often has difficulty awaiting turn”, “often blurts out answers before questions have been completed”, and “often interrupts or intrudes on others” may also be explained by the DTD theory, since these symptoms involve a delay between the target behaviour and the actual reinforcement. Therefore, they may be interpreted as due to abnormal sensitivity to delay of reinforcement arising from a failure of the transfer of dopamine cell firing activity in response to cues that predict reinforcement.

The remaining DSM IV symptoms of hyperactivity and impulsivity do not lend themselves to obvious interpretation in terms of the DTD theory. These are “often fidgets with hands or feet or squirms in seat”, “often has difficulty playing or engaging in leisure activities quietly”, “is often ‘on the go’ or acts as if ‘driven by a motor’”, and “often talks excessively”. These symptoms may involve motor activating effects of dopamine due to modulation of

excitability of striatal neurons (Bolam et al., 2006; Nicola et al., 2000; Wickens, 1990).

In addition to suggesting a possible mechanism for symptoms, the DTD theory suggests a possible mechanism of action for methylphenidate, which will be considered in the next section.

6. Therapeutic mechanism of methylphenidate

The precise mechanism by which methylphenidate exerts its therapeutic effects is not known. A number of theories exist which differ in the neurotransmitter or the direction of effect. Levy (1991) proposed that methylphenidate corrected an underlying deficit of dopamine, and that methylphenidate worked by increasing the impulse-associated release of dopamine. Others proposed that stimulants would function as antagonists (Solanto, 2002). Some theories argue for an involvement of norepinephrine (Arnsten, 2006; Pliszka et al., 1996) or serotonin (Gainetdinov et al., 1999). Here we focus on methylphenidate actions on dopamine in relation to the DTD theory.

Volkow et al. (1998) showed that a standard clinical dose of 0.5 mg/kg methylphenidate would block about 60% or more of DAT, indicating a strong affinity for DAT in the brain, and a mechanism of action like cocaine. PET imaging using [(11)C]raclopride showed that this would result in increased occupancy of extrasynaptic dopamine D2 receptors. [(11)C]raclopride is a dopamine D2 receptor radioligand that competes with endogenous dopamine for occupancy of the D2 receptors, so its displacement is a measure of extracellular dopamine. Changes in [(11)C]raclopride binding have been shown to be linearly related to microdialysis measures of extracellular dopamine (Breier et al., 1997) but the relationship is complicated by other factors such as internalization of receptors (Laruelle and Huang, 2001). Despite the low sensitivity of the method, studies support the view that clinically relevant doses of methylphenidate produce their therapeutic effects by increasing extracellular dopamine (Rosa Neto et al., 2002; Volkow et al., 2002, 1999). However, we think it is important to note that this does not necessarily mean that there is an underlying dopamine deficiency in ADHD – although it is a possibility – since PET does not provide a direct measure of the basal level of extracellular dopamine.

The DTD theory proposes that methylphenidate exerts its therapeutic effects by increasing the magnitude of the anticipatory dopamine cell response to predictive cues. Consistent with this hypothesized mechanism of action, methylphenidate selectively increases the efficacy of conditioned reinforcers (Hill, 1970; Robbins, 1975, 1978). These findings are consistent with facilitation of dopamine release in response to predictive cues by methylphenidate.

In the context of the DTD theory, the facilitation of the response to predictive cues by methylphenidate suggests a possible basis for its therapeutic effects in children with ADHD. Specifically, methylphenidate should reduce the effect of delay of reinforcement by amplifying the effects of “bridging” cues. Consistent with this idea, Wade et al. (2000) have shown that *D*-amphetamine, which has similar effects to methylphenidate, increases preference for delayed reinforcers. In rats, Cardinal et al. (2000) showed that this increased preference for delayed reinforcers only occurs when the delay is signalled.

Clearly, further work is needed to elucidate the pathophysiological mechanisms of ADHD, and the therapeutic actions of methylphenidate.

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