
11 Functional Neuroimaging of Reward and Motivational Pathways in ADHD

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11.1 OVERVIEW

The evolving field of research on Attention-Deficit/Hyperactivity Disorder (ADHD) has now moved beyond the search for a common core dysfunction towards a recognition of ADHD as a heterogeneous disorder of multiple neuropsychological deficits and hypothesised causal substrates (e.g. Faraone & Biederman, 1998; Todd, 2000; Nigg, 2001; Castellanos & Tannock, 2002; Sonuga-Barke, 2002, 2003). The variety of topics and research areas covered by the chapters of this book attests to this important theoretical and empirical progression but also to the realisation of the complexity implied by such an undertaking.

That ADHD is a heterogeneous disorder is apparent at almost every level of analysis, from the implication of multiple genes (Chapters 7, 8 and 10), the identification of multiple sites of neural dysfunction (Chapters 12 and 14), and a wide range and varying degrees of cognitive deficits (Chapters 12 and 17); to vast differences in the behavioural expression of the disorder, including clinical presentation (Chapters 2 and 3), to variation in response to treatment, particularly drug treatments such as methylphenidate (Chapters 13 and 15). This phenotypic, genetic and neuropsychological heterogeneity poses a formidable challenge as investigators attempt to discern the many factors that contribute to the development and expression of ADHD. Indeed, subtypes based on the DSM-IV symptom dimensions of Inattention or Hyperactivity/Impulsivity have not proved to be particularly fruitful means of clarifying neurobiological or nosological questions. Translational approaches, such as the pursuit of endophenotypes, have been suggested as a strategy to delineate putative causal mechanisms that may serve to organise our clinical and neuroscientific perspectives in a manner similar to that used to organise the

Periodic Table of the Elements based on their fundamental physical and chemical properties (Castellanos & Tannock, 2002, see also Chapter 12). Although attempting to assemble even a preliminary 'Table of Neurocognitive Elements' is premature, we believe that we can start on this ambitious agenda by building on the advances emerging from basic neuroscience and imaging studies. One area which may prove particularly fruitful is the investigation of how variations in the circuitry and the cellular and molecular mechanisms involved in motivational processes are linked to the symptoms of ADHD or underlying genetic risk factors. This chapter will focus on delineating such mechanisms and their relevance to understanding ADHD.

11.2 EXECUTIVE DYSFUNCTION AND EVOLVING NEUROCOGNITIVE MODELS OF ADHD

ADHD research over the past decade was energised by the hypothesis that deficits in executive function (EF), in particular, inhibitory control, form the core neurocognitive deficit in ADHD (Barkley, 1997). However, the substantial resulting literature (as reviewed by Homack & Riccio, 2004; Romine *et al.*, 2004; Boonstra *et al.*, 2005; Martinussen *et al.*, 2005; van Mourik *et al.*, 2005; Willcutt *et al.*, 2005) demonstrates that no specific EF deficit is sufficient to account for dysfunction across all or most individuals with ADHD (Nigg *et al.*, 2005). Quantitatively, the explanatory power of single EF deficits calculated using meta-analytic techniques demonstrates that the association between ADHD diagnosis and deficits in planning, attention switching, working memory, or sustained attention is moderate at best (Nigg *et al.*, 2005; Willcutt *et al.*, 2005; Castellanos *et al.*, 2006). For example, Nigg *et al.* (2005) reviewed the evidence for executive dysfunction in ADHD across three samples comprising almost 900 children, about one-third of whom were children with combined type ADHD and two-thirds controls. They examined performance on several neuropsychological measures of EF including the Stop Signal Reaction Time (SSRT), Reaction Time variability, and performance on the Stroop, Continuous Performance and Trailmaking tasks. Task measures were clustered to assess dysfunction on the putative executive functions of inhibitory control, vigilance/sustained attention, and attentional control. Defining 'abnormal' or 'impaired' performance on a given neuropsychological measure as performance worse than that of 90% of control subjects (i.e. below the 10th percentile, see Figure 11.1(i)), they observed that no more than half of the children with ADHD could be classified as 'impaired'. More specifically, on one of the most frequently used measures of inhibitory EF deficit in ADHD, the SSRT, fewer than 50% of the total ADHD sample were 'impaired' in their performance (see Figure 11.1(ii)). Furthermore, while nearly 80% of children with ADHD demonstrated a deficit on at least one EF measure, the same was true of almost 50% of control subjects (Nigg *et al.*, 2005). The authors conclude that while between 35% and 50% of children with combined type ADHD exhibit impaired performance on common neuropsychological tests of EF (as defined by control sample performance), the remaining 50% to 65% of children with the diagnosis do not.

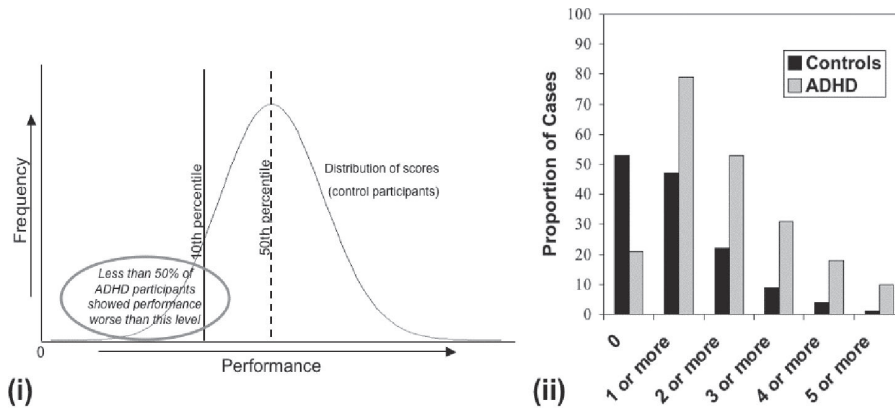


Figure 11.1. (i) Schematic representation of the distribution of scores and performance percentiles on any given measure and (ii) the proportion of Control and ADHD participants demonstrating performance above the 10th percentile on different numbers of EF tasks (based on Nigg *et al.*, 2005)

11.2.1 MULTIPLE PATHWAYS TO DYSFUNCTION: ‘HOT’ AND ‘COOL’ EXECUTIVE FUNCTION

In response to evidence for the cognitive and neurobiological heterogeneity of ADHD, an alternative view emphasising multiple etiologic ‘pathways’ in ADHD has been proposed by a number of investigators (Sonuga-Barke, 2002, 2003, 2005; Nigg *et al.*, 2005). This view suggests that the causal substrates of ADHD comprise multiple neural pathways that are dissociable anatomically and neuropsychologically. In the earliest version of such a model, Sonuga-Barke proposed that a minimum of two pathways would be necessary to account for ADHD (Sonuga-Barke, 2002, 2003). Accordingly termed the ‘dual pathway’ model, it posits that deficits in executive processes are mediated through ventrolateral and dorsolateral cortical-striatal circuitry, and are distinct from differences in motivational performance, which are mediated by mesolimbic (medial and orbital prefrontal) ventral striatal circuits. Support for this model is provided by studies demonstrating that cognitive deficits such as inhibition are distinct from (i.e., uncorrelated with) the tendency to choose a smaller immediate reward rather than a larger delayed reward (Solanto *et al.*, 2001; Sonuga-Barke *et al.*, 2003). The dual pathway model maps onto and supports the distinction between ‘hot’ and ‘cool’ executive function in ADHD cognition and in development (Zelazo *et al.*, 2002). ‘Cool’ executive function (EF) refers to top-down processes that are relatively purely cognitive in nature, which are typically elicited by abstract, decontextualised problems. Examples of ‘cool’ EF include working memory, sustained attention, or task set switching. In contrast, ‘hot’ EF refers to cognitive processes that also have an affective, motivational, or incentive/reward component, and include processes such as affective decision-making (e.g. decision-making under conditions of risk). ‘Hot’ EF comprises both top-down and bottom-up processes, although the latter are likely to weigh more heavily in ‘hot’ EF than in circumstances that evoke ‘cool’ EF.

While EF in general is purported to rely on discrete cortico-striatal-thalamo-cortical loops (Alexander *et al.*, 1986; McFarland & Haber, 2002; Heyder *et al.*, 2004; Chudasama & Robbins, 2006), 'cool' and 'hot' aspects of EF may be dissociated according to the trajectory of their associated neural pathways. Thus, 'cool' EF is primarily subserved by a dorsal pathway connecting the thalamus and the dorsal striatum to lateral (including inferior prefrontal) and dorsolateral PFC, while 'hot' EF is mediated by more ventromedial pathways connecting mesolimbic reward circuitry, including the amygdala and ventral striatum, to orbitofrontal and medial PFC (Haber *et al.*, 2000; Haber, 2003). The distinction between dorsal and ventral pathways is admittedly simplistic. Clearly, 'cool' EF comprises a range of cognitive functions, which may be dissociated based on their functional localisation to various portions of frontal cortex. For example, 'cool' functions such as working memory (e.g. d'Esposito *et al.*, 2000; Curtis & d'Esposito, 2003) and inhibition (e.g. Aron *et al.*, 2004; Chambers *et al.*, 2005) are differentially localised to dorsal and ventral portions of the lateral surface of the frontal lobes, with further differentiation associated with the component processes of those functions (e.g. maintenance and manipulation in working memory). There is a similar diversity of 'hot' executive functions, which reflect the interaction of top-down processes associated with orbital and ventromedial PFC and more primitive, bottom-up motivational mechanisms involved in mediating the effects of rewards and punishments, linked to the ventral striatum.

Pervasive 'cool' EF deficits, which are present in a subset of children with ADHD (Nigg *et al.*, 2005; Willcutt *et al.*, 2005), are thus likely to be closely linked to dysfunction in regions of the frontostriatal pathway, such as dorsolateral or ventrolateral prefrontal cortex (dlPFC, vlPFC) and anterior/dorsal regions of caudate and putamen. Conversely, dysfunction in regions such as the ventral striatum or amygdala may adversely affect bottom-up 'hot' motivational processes, reflected in abnormalities in sensitivity to performance incentives (rewards), temporal delays before receipt of rewards (Delay Aversion), and environmental cues. These abnormalities in turn can impact top-down cognitive processes to produce deficits in 'hot' EF. As a consequence of these theoretically dissociable paths for dysfunction, and consistent with the empirical evidence suggesting heterogeneity of neuropsychological deficits in ADHD, individuals with ADHD may be expected to manifest varying degrees of deficits, reflecting primarily cognitive dysfunction, primarily motivational dysfunction, or a combination of these. Because distinctions between 'hot' and 'cool' are a matter of degree rather than being clearly demarcated, dysfunctional interactions between cognitive and motivational processes are perhaps particularly likely, and successful goal-directed behaviour is likely to require a combination of effective 'hot' and 'cool' EF (Hongwanishkul *et al.*, 2005).

The predominant focus of ADHD research has been on 'cool' EF, assessed by tasks such as Continuous Performance Tasks (CPT), GO/NOGO, Stop task (the SSRT measure), Stroop, Eriksen Flanker, and working memory tasks (Homack & Riccio, 2004; Romine *et al.*, 2004; Boonstra *et al.*, 2005; Martinussen *et al.*, 2005; van Mourik *et al.*, 2005) and studies have demonstrated that specific 'cool' EF deficits are associated with dysfunction in particular regions of the dorsal frontostriatal pathway, including the anterior cingulate cortex (Bush *et al.*, 1999), the caudate and

putamen (Casey *et al.*, 1997; Durston *et al.*, 2003; Vaidya *et al.*, 2005) and ventral prefrontal cortex/inferior frontal gyrus (Aron & Poldrack, 2005; Rubia *et al.*, 2005). These studies have contributed considerably to the view that ADHD is a neurobiologically and neuropsychologically heterogeneous disorder, and to the recognition that individuals with ADHD will demonstrate varying degree of impairment in these 'cool' executive functions (e.g. Nigg, 2005; Nigg *et al.*, 2005). Furthermore, these studies have spurred progress in the search for endophenotypes for ADHD, with the proposal of several 'cool' executive functions as candidate endophenotypes, including inhibition (Slaats-Willems *et al.*, 2003; Aron & Poldrack, 2005), working memory (Castellanos & Tannock, 2002; Westerberg *et al.*, 2004), reaction time variability (Manor *et al.*, 2002; Toplak *et al.*, 2003; Castellanos *et al.*, 2005), and sustained attention (Chapter 12).

In contrast to recent progress in delineating the role of 'cool' executive functions and their corresponding neurobiological substrates in ADHD, 'hot' EF in ADHD remains relatively unexplored. A notable exception has been the theory articulated by Sagvolden *et al.* (2005) which hypothesises that the full range of combined type ADHD symptoms can be traced to a hypofunctioning dopaminergic system that results in a shorter and steeper delay-of-reinforcement gradient and deficient behavioural extinction. Their 'dynamic developmental theory' is grounded primarily in basic science observations gleaned from study of the spontaneously hypertensive rat (SHR). This translational model provides an ambitious framework within which many methodological and conceptual issues remain to be fully articulated, as pointed out in many of the accompanying commentaries and responses to the Sagvolden *et al.* (2005) paper. In addition, the theory is partially, but not wholly supported by data from studies of the SHR (e.g. Johansen and Sagvolden, 2005a, 2005b; Johansen *et al.*, 2005). While we are enthusiastic regarding the long-term value and importance of translational research in bridging from rodent model systems to human symptomatology and vice-versa, the availability of neuroimaging techniques also provides heretofore unavailable access to neuroanatomic structure and cerebral function in humans. In this chapter, we will focus on the neural substrates of bottom-up reward and reinforcement processing, examining the behavioural, functional and anatomic evidence for the role of dysfunction in these motivational processes in ADHD, in light of emerging perspectives from basic neuroscience, neuropsychological studies, and functional neuroimaging.

11.2.2 'HOT' MOTIVATIONAL FUNCTIONS: REWARD AND DELAY

The notion that ADHD is secondary to abnormalities in reward-related circuitry has a long history (Wender, 1972; Douglas & Parry, 1983; Haenlein & Caul, 1987; Iaboni *et al.*, 1997; Sagvolden *et al.*, 1998; Douglas, 1999; Tripp & Alsop, 1999, 2001; Blum *et al.*, 2000; Castellanos & Tannock, 2002; Sonuga-Barke, 2002, 2003, 2005; Ernst *et al.*, 2003; Sagvolden *et al.*, 2005). However, empirical evidence for this hypothesis remains somewhat equivocal. There are many different aspects to reward such as magnitude, immediacy, and probability (Williams & Taylor, 2004), and the contribution of each of these aspects to reward sensitivity in ADHD has not been studied comprehensively. While some studies (e.g. Douglas & Parry, 1983; Douglas,

1999) have suggested that children with ADHD are unusually sensitive to rewards, behavioural studies of reward sensitivity in ADHD have not yielded consistent group differences in behavioural facilitation or suppression as a result of rewards or punishments. A qualitative review of this literature was recently provided by Luman *et al.* (2005) and is briefly summarised here.

Luman *et al.* (2005) examined 22 studies, comprising behavioural data collected from almost 1200 children, which compared ADHD and control participants on tasks involving rewards and punishments, in order to chart the behavioural effects of reinforcement contingencies in ADHD. Just over half of the studies reviewed demonstrated a differential effect of reward contingencies on performance between ADHD and control groups, suggesting a greater positive impact of reward on performance in ADHD participants, relative to control participants. Interestingly, a number of studies that included physiological measures of heart rate and skin conductance suggested that children with ADHD were generally psychophysiologicaly *less sensitive* to reinforcement contingencies than control children. Overall, the picture provided by Luman *et al.* is that of a complex literature that does not provide clear support for, nor clear evidence against, a role for dysfunctional reward and motivational processing in ADHD.

Given the wide range of paradigms, measures, and methods used, it should not be surprising that the ADHD reward literature is mostly inconclusive (Luman *et al.*, 2005). The most consistent finding in the 'hot' motivational domain that has been identified is the preference for immediate over delayed rewards exhibited by individuals with ADHD relative to controls (Rappoport *et al.*, 1986; Sonuga-Barke *et al.*, 1992; Schweitzer & Sulzer-Azaroff, 1995; Barkley *et al.*, 2001; Kuntsi *et al.*, 2001; Solanto *et al.*, 2001; Tripp & Alsop, 2001, Luman *et al.*, 2005; Bitsakou *et al.*, 2006; but also see negative reports, e.g. Scheres *et al.*, in press). These studies have generally found that children with ADHD prefer rewards that minimise time on task while control children tend to maximise their total reward. That is, children with ADHD demonstrate a hypersensitivity to reward-related delay and delay-predictive cues, and difficulties in waiting and working for rewards. This leads them to escape or avoid delay when they can (Solanto *et al.*, 2001; Sonuga-Barke *et al.*, 2004), a tendency that has been termed *Delay Aversion* (Sonuga-Barke *et al.*, 1992; Sonuga-Barke, 2002). Like deficits in 'cool' EF, Delay Aversion has been linked to putative alterations in dopamine-modulated basal ganglia/anterior cortical circuits (Sagvolden *et al.*, 2005), but in the distinct 'hot' EF circuit that links the ventral striatum to ventromedial and orbitofrontal cortex (Sonuga-Barke, 2005). To our knowledge, however, this link has not been explicitly assessed on a neurobiological level.

Clearly, the examination of reward-related processing in ADHD is complex, a fact that is reflected in discrepancies and inconsistencies in results across studies. In addition, we currently lack empirical knowledge concerning the functioning of the neurobiological substrates of reward-related processing in ADHD. As a result, the neural foci of motivational processes, such as Delay Aversion have yet to be identified experimentally. *We suggest that what has been lacking in this research area is an attempt to explicitly probe the neural circuitry underlying task performance.* We suggest that the use of neuroimaging techniques to probe the neural circuitry underlying reward-related processing in ADHD constitutes an important step towards an

empirical delineation of the neurobiological substrates of reward-related processing in ADHD.

11.3 THE NEURAL CIRCUITRY OF REWARD

Broadly defined, rewarding stimuli are those an organism will work to attain. The brain regions most commonly activated by rewarding stimuli include the midbrain, ventral and dorsal striatum (including the nucleus accumbens – NAcc), amygdala, orbitofrontal cortex (OFC) and other areas of prefrontal cortex (PFC) (McClure *et al.*, 2004b; Knutson & Cooper, 2005) and may be considered nodes of a motivational processing pathway. Goal-directed behaviour is mediated by information processing in several parallel thalamo-cortico-striatal loops which begin with mid-brain dopaminergic neurons in the substantia nigra and ventral tegmental area and spiral through the striatum and thalamus to areas of frontal cortex (Alexander *et al.*, 1986; Alexander & Crutcher, 1990; Haber *et al.*, 2000; Schultz, 2002; Haber, 2003). These ascending circuits may be differentiated into ‘hot’ and ‘cool’ processing pathways on the basis of their functional projections, with connections between ventral striatum and areas of orbital and medial frontal cortex forming a pathway for motivational processing (Haber *et al.*, 2000). The basal ganglia are a crucial component of these neural pathways, linking two neural circuits. A striato-nigral-striatal network circuit channels information flow between ventromedial (limbic) central (associative) and dorsolateral (motor) regions of the striatum, while a thalamo-cortical-thalamic network relays information to the cortex. Within each of these networks, information is channeled from limbic to cognitive to motor circuits (Haber, 2003). This pattern of information flow and the interactions between the parallel pathways provide a basis through which emotion/motivation related ‘hot’ pathways influence ‘cool’ cognitive pathways, which, in turn, influence behaviour through their input to motor pathways (see Figure 11.2).

In this section, we will first focus on the functions of the bottom-up ‘hot’ motivational pathway centred on the ventral striatum. Later in the chapter, we will discuss the top-down processing pathways and their interactions. It is important to mention that while we focus on the role of dopamine in reward-related process, a clear role for other neurotransmitters, such as serotonin, has also been demonstrated (e.g. Robbins, 2005; Chudasama & Robbins, in press). However, dopamine has been identified as having a central role in the pathophysiology of ADHD (e.g. Sagvolden & Sergeant, 1998; Biederman & Faraone, 2002; Castellanos & Tannock, 2002; Sagvolden *et al.*, 2005).

11.3.1 DOPAMINE AND BOTTOM-UP REWARD SIGNALS: INCENTIVE SALIENCE AND REWARD ANTICIPATION

The seminal work of Schultz and colleagues (Schultz & Romo, 1990; Schultz *et al.*, 1993; Hollerman & Schultz, 1998; Schultz, 1998, 2001, 2002; Schultz *et al.*, 1998) established that midbrain dopamine (DA) neurons code for rewarding stimuli by demonstrating brief increases in phasic activation following the occurrence of rewards. Importantly, this response is only observed when rewards are different

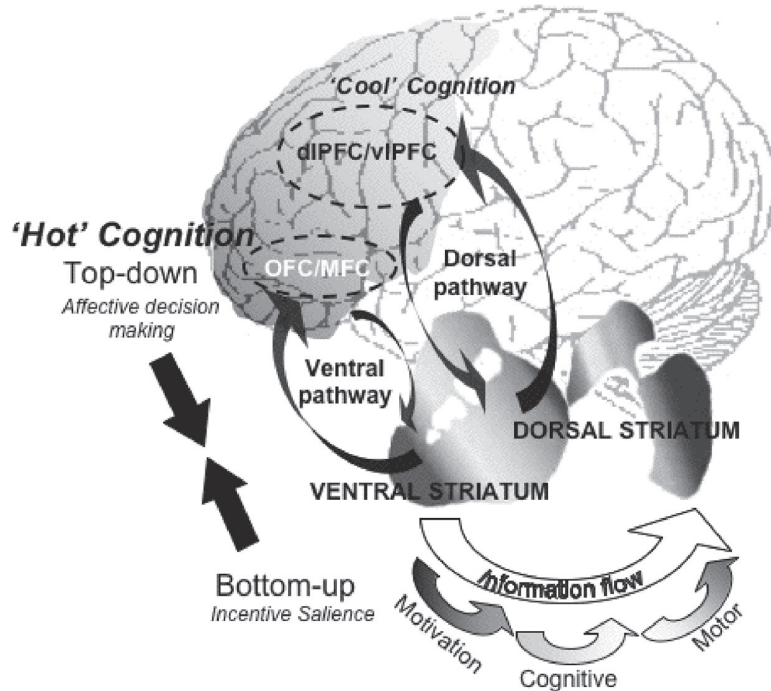


Figure 11.2. Schematic model of the dorsal and ventral neural pathways associated with 'Cool' and 'Hot' cognition

from predictions. That is, there is a change in the phasic activity of DA neurons when there is a discrepancy or 'error' between the prediction of the reward and its occurrence. This change in phasic activity is termed the 'reward prediction error' (Schultz, 1998). When a reward occurs that is unpredicted, the prediction error is positive and is signalled by an increase in DA activity. If a predicted reward is omitted, the prediction error is negative (activation is depressed). Experimental work has shown that this depression in DA firing occurs when animals fail to obtain reward because of erroneous behaviour, when reward delivery is blocked, or when reward delivery is unexpectedly delayed (Schultz *et al.*, 1993; Hollerman & Schultz, 1998; Schultz, 2002). The reward prediction error thus functions as an important behavioural learning signal that *indicates the need to modify behaviour in order to reduce the discrepancy between predictions and outcomes* (Schultz, 2001). Predictions and behaviour continue to change on the basis of the reward prediction error signal until the outcome occurs as predicted (i.e. learning asymptotes), at which time the prediction error becomes zero (Schultz, 2001).

An important characteristic of the reward prediction error signal is that, during learning, the response transfers from the reward itself to reward-predicting stimuli (cues) (Schultz *et al.*, 1998). That is, DA neurons (particularly afferents to the ventral striatum) signal the *anticipation* of a possible reward by responding to cues that predict the occurrence of the reward, rather than the occurrence of the reward

itself (Schultz, 2001). The DA reward prediction error thus appears to constitute a bottom-up signal that assigns 'incentive salience', or motivational value to objects and actions. Incentive salience is then used in action selection such that more valuable actions are more likely to be selected (McClure *et al.*, 2003). In order to be useful for behaviour, however, incentive salience needs to be supplemented by additional information. Neurons in other regions of the striatum, in the frontal cortex and amygdala also process reward information and provide more differentiated information for identifying and anticipating rewards and organising goal-directed behaviour (Schultz, 2002). In particular, the OFC appears to discriminate between different types of rewards; neurons in the OFC respond differentially to preferred versus non-preferred rewards (Critchley & Rolls, 1996; Tremblay & Schultz, 1999; Padoa-Schioppa & Assad, 2006), suggesting that OFC neurons contribute to the 'liking' (hedonic) component of reward-seeking behaviour. Regions of orbitofrontal and ventromedial frontal cortex also show activation during the outcome period of a reward task (e.g. Knutson *et al.*, 2001b), showing greater activation for positive than negative outcomes (Knutson *et al.*, 2003; O'Doherty *et al.*, 2003a; Rogers *et al.*, 2004), suggesting that these areas also perform an evaluative role. In contrast, neurons in the midbrain and ventral and dorsal striatum do not appear to discriminate between different rewards or signal the pleasure associated with a particular reward, but instead provide the 'wanting' component, the motivational component of reward-seeking behaviour (McClure *et al.*, 2003; Schultz, 2002). This bottom-up motivational signal provided by the activity of DA neurons in the midbrain and striatum then influences pathways involved in higher cognitive processes by means of interactions between ascending thalamo-cortico-striatal loops projecting to areas of PFC (Schultz, 2001; Haber, 2003). It is in this way that bottom-up DA reward signals interact with top-down signals from other areas of the brain to produce successful goal-directed behaviour.

11.3.2 HUMAN NEUROIMAGING STUDIES OF BOTTOM-UP REWARD-RELATED PROCESSING

While the foundational work in this area was carried out with animals such as rats and non-human primates, recent investigations have observed the reward prediction error response in humans using fMRI (Knutson *et al.*, 2000; Berns *et al.*, 2001; McClure *et al.*, 2003). By examining changes in activation in the brain during performance of a task in which participants work to receive a reward, an increase in activation in areas of the mesolimbic reward circuit, including the ventral striatum/NAcc and amygdala, has been observed to coincide with the occurrence of the reward, while a depression of activation occurs when an expected reward is omitted (Delgado *et al.*, 2000; Berns *et al.*, 2001; McClure *et al.*, 2003; Ramnani *et al.*, 2004; Ernst *et al.*, 2005). These responses were observed regardless of whether the reward is a primary stimulus such as food, or a conditioned reward such as money. Reward-related activation in the ventral striatum/NAcc has also been observed to scale with reward magnitude, with more activation being associated with larger rewards (Knutson *et al.*, 2001a; Galvan *et al.*, 2005; Knutson *et al.*, 2005).

More recently, studies have focused on the transfer of incentive salience activation from the time of reward occurrence to reward-predicting cues, a response that

has been termed 'reward anticipation' (Knutson *et al.*, 2001a; Pagnoni *et al.*, 2002; McClure *et al.*, 2003; O'Doherty *et al.*, 2003b; Galvan *et al.*, 2005). This work is based on Schultz's (2001) observation that DA neurons (particularly in the ventral striatum) signal the anticipation of a possible reward, rather than the delivery of the reward itself. For example, Knutson and colleagues (Knutson *et al.*, 2001b) examined activations related to reward anticipation as distinct from reward delivery with fMRI in normal adult volunteers. Participants were first presented with a cue that signalled either a potentially rewarded response, an unrewarded response, or no response requirement. In reward trials, participants were then required to respond to a target while it was on screen in order to receive the monetary reward. In the non-rewarding trials, there was no reward, regardless of the response, and in the non-response trials, participants were required to refrain from responding. Feedback regarding success (win/no win) on that trial was then provided.

By examining separately activation related to the cue presentation and activation related to feedback, Knutson *et al.* (2001b) were able to dissociate activations related to reward anticipation and reward outcome. They observed robust activations associated with reward anticipation in the NAcc while reward delivery was associated with activation in the ventral medial prefrontal cortex. Activation in the NAcc was depressed when a reward was omitted because a participant had failed to respond in time, consistent with Schultz's observation of a negative reward error signal. These and similar findings have been repeated in several other neuroimaging studies (e.g. Knutson *et al.*, 2001a; O'Doherty *et al.*, 2002; Pagnoni *et al.*, 2002; McClure *et al.*, 2004b; O'Doherty, 2004).

11.3.3 THE VENTRAL STRIATUM MAINTAINS INCENTIVE SALIENCE OVER DELAYS

The neuroimaging studies of reward anticipation discussed in the preceding paragraphs suggest that the ventral striatum, the NAcc in particular, is a crucial structure in the brain's response to delayed rewards, through the anticipatory activity of DA neurons. Given the robust behavioural evidence for Delay Aversion in ADHD (e.g. Sonuga-Barke *et al.*, 1992; Barkley *et al.*, 2001; Kuntsi *et al.*, 2001; Solanto *et al.*, 2001; Tripp & Alsop, 2001; Bitsakou *et al.*, 2006), the investigation of the effects of delayed reward on ventral striatal/NAcc neurons should be informative to our understanding of the disorder.

Models of the relationship between dysfunctional reward circuitry and symptoms such as Delay Aversion provide a framework for such investigations. As discussed earlier in this chapter, Sagvolden *et al.* (e.g. Sagvolden *et al.*, 1998; Johansen *et al.*, 2002; Sagvolden *et al.*, 2005) have proposed a comprehensive theory of ADHD which hypothesises that hypofunctioning dopamine systems give rise to the altered reinforcement processes, deficient attentional responses and poor executive functioning that underlie a majority of the behavioural symptoms associated with the disorder. More specifically, the theory proposes that hypofunction of the mesolimbic DA reward system, and consequent low levels of DA activity in areas such as the NAcc, results in altered reinforcement processes, which take the form of a shorter and steeper delay-of-reinforcement gradient, and deficient behavioural

extinction. This predicts that the time window within which a behaviour will become associated with its consequences (e.g., a reward) is shortened in children with ADHD, giving rise to impulsiveness. Delay Aversion in ADHD is suggested to be a result of this shorter delay-of-reinforcement gradient, as even short delays between a behaviour and its reward may be too long to reinforce the behaviour (Sagvolden *et al.*, 2005).

While the dynamic developmental theory (Sagvolden *et al.*, 2005) hypothesises a link between reduced DA activity, a shorter delay-of-reinforcement gradient and Delay Aversion in ADHD, it does not explicitly associate deficient reward-related *anticipatory* activity in areas such as the NAcc with Delay Aversion. In a model that makes this potential link explicit, Tripp & Wickens (Wickens & Tripp, 2005) have proposed that in children with ADHD, the DA reward anticipation signal is diminished. They suggest that the transfer of the DA response from a reward to its predictive cue fails to develop normally in children with ADHD. This means that the delay-bridging anticipatory activity of DA cells is weaker for children with ADHD than for normal children, making them increasingly likely to engage in behaviours that result in immediate reinforcement (e.g. choosing the smaller, immediate reward).

While the two theories vary somewhat in the perspective within which they frame predictions, they have in common a hypothesised link between hypofunctioning mesolimbic reward circuitry (particularly reduced DA activity in the NAcc) in ADHD and behavioural phenomena such as Delay Aversion. Despite the evidence supporting dysfunction of prefrontal cortical-striatal circuitry provided by neuroimaging investigations of ADHD (Aylward *et al.*, 1996; Castellanos *et al.*, 1996; Casey *et al.*, 1997; Filipek *et al.*, 1997; Mataro *et al.*, 1997; Bush *et al.*, 1999; Rubia *et al.*, 1999; Teicher *et al.*, 2000; Durston *et al.*, 2003), the neural circuitry underlying motivational phenomena such as Delay Aversion in ADHD has not been directly assessed using neuroimaging. The failure to probe the neural substrates of reward using neurobiologically informed paradigms may account in part for our difficulty in resolving the question of precisely how reward-related neuronal systems are abnormal in ADHD. Nonetheless, the development of theories concerning the role of dysfunctional reward circuitry in ADHD, such as those of Sagvolden *et al.* (Sagvolden *et al.*, 1998; Sagvolden *et al.*, 2005), Sonuga-Barke (Sonuga-Barke, 2002, 2003), and Wickens and Tripp (Wickens & Tripp, 2005), set out a clear research path for neuroimaging assays of their hypotheses.

The translational nature of this approach suggests this will be a fruitful research path. Studies have demonstrated that lesions to the NAcc cause rats and chickens to prefer small immediate rewards to larger delayed rewards (Cardinal *et al.*, 2001; Cardinal *et al.*, 2002; Izawa *et al.*, 2005). A lesion to the NAcc core similarly impaired instrumental learning in rats when reinforcement was delayed and also impaired performance of a previously learned instrumental response when reinforcement was delayed (Cardinal & Cheung, 2005). In light of these findings, Cardinal and colleagues propose that the function of the NAcc is to bridge action-outcome delays – both during and subsequent to learning. That is, they suggest that the NAcc maintains a working memory-type representation of incentive salience over a delay, in order to facilitate reward-seeking behaviour. It is this delay-bridging maintenance

of incentive salience that is proposed to be diminished in ADHD (Wickens & Tripp, 2005). In the following sections, we highlight what we believe are the salient research questions and hypotheses that can be addressed by pursuing these links through neuroimaging examinations of reward and delay-related processing in ADHD.

11.4 NEW RESEARCH DIRECTIONS

The preceding discussion prompts us to assert that the investigation of the neural circuitry of reward processing in ADHD represents a fruitful avenue of research, one which has the potential to both generate and answer a new set of questions about the dysfunctions that might underpin 'hot' motivational aspects of cognition in ADHD.

11.4.1 NEUROIMAGING OF INCENTIVE SALIENCE AND REWARD ANTICIPATION IN ADHD

One of the principal research questions is whether there are differences in brain activations related to reward processing between ADHD and normal individuals? Scheres *et al.* (in press) recently addressed this question by using fMRI to examine the areas activated when adolescents with and without ADHD performed the reward-anticipation paradigm developed by Knutson *et al.* (Knutson *et al.*, 2000, 2001a, 2001b). The ADHD group comprised six adolescents with combined-type ADHD and five with inattentive-type ADHD, and there were eleven gender-, age- and IQ-matched healthy controls. The hypothesis that the ADHD and control groups would differ in the magnitude of striatal activation during reward anticipation was supported. Relative to controls, adolescents with ADHD demonstrated reduced ventral striatal activation during reward anticipation, and this reduction became more pronounced with increasing reward magnitudes (20c – \$1 – \$5). In addition, a significant negative correlation was observed between ventral striatal activation and levels of hyperactivity/impulsivity in the sample as a whole (i.e. including both ADHD and control participants), while no such correlation was found for symptoms of inattention. These findings provide preliminary support for the hypothesis that ADHD is associated with hyporesponsiveness of the ventral striatum during reward anticipation, and further, suggest that this hyporesponsiveness is specifically related to hyperactive/impulsive behaviours.

It is possible that the ventral striatal hyporesponsiveness observed in the ADHD group is the result of a dopaminergic deficiency in the mesolimbic circuit, which may have acted to diminish the perceived saliency of anticipated rewards in the ADHD sample (Johansen *et al.*, 2002; Volkow *et al.*, 2004). This hypothesis is consistent with a study (Ernst *et al.*, 1999) which examined midbrain dopaminergic activity in children with ADHD using pharmacological PET and the dopaminergic tracer fluoro-DOPA ($[^{18}\text{F}]\text{DOPA}$). This tracer is an analogue of dihydroxyphenylalanine (DOPA), the DA precursor, and imaging the tracer using PET provides information on DA synthesis and storage processes (Ernst *et al.*, 1999). High accumulations of the tracer were observed in the right midbrain of children with ADHD, and higher levels of the tracer were associated with increased symptom

severity. High levels of [¹⁸F]DOPA indicate enhanced DA synthesis, which could reflect a number of processes: higher enzyme activity, increased density of DA cell bodies and terminals, or both (Ernst *et al.*, 1999). Ernst *et al.* note that this kind of enhanced activity has been observed previously in response to low extracellular levels of DA (Abercrombie *et al.*, 1990; Torstenson *et al.*, 1997), and to the blockade of DA receptors (Hadjiconstantinou *et al.*, 1993; Zhu *et al.*, 1993). Replication of such findings is essentially impossible given current trends in research ethics (Wendler *et al.*, 2005), which makes it difficult to determine how to integrate these data with recent findings which suggest that ADHD in adults is associated with increased striatal DAT density (Spencer *et al.*, 2005), and the observation that therapeutic doses of methylphenidate increase the concentration of dopamine in striatum by blocking DAT (Volkow *et al.*, 2001). Finally, methylphenidate has been shown to increase extracellular levels of dopamine in striatum during math test performance in ADHD, in association with increased motivation (Volkow *et al.*, 2004). One way in which this dopamine hypothesis could be addressed indirectly in children would be to assess the effects of stimulant administration on activation in the ventral striatum during reward anticipation in participants with ADHD.

11.4.2 NEUROIMAGING OF DELAY AVERSION

In addition to providing encouraging support for the hypothesis that reward-related processing is dysfunctional in ADHD, Scheres *et al.*'s findings provide a basis from which to develop further research questions and hypotheses. One such question is, what is the interaction between incentive salience and delay? If we take the view, outlined in the previous section, that the ventral striatum/NAcc serves to maintain a working memory-type representation of incentive salience, what might be the impact of delay on ventral striatal activation? Might Delay Aversion in ADHD be related to a weaker/more rapidly dissipating signal in the ventral striatum/NAcc over a delay imposed prior to reward presentation, as has been suggested (e.g. Wickens & Tripp, 2005)? What is the effect of uncertain delays or rewards? Such questions might be investigated using a reward anticipation paradigm (e.g. one based on the work of Knutson and colleagues), combined with an immediate/delayed reward manipulation. While we believe this approach may be informative with regard to the neural bases of reward processing and Delay Aversion in ADHD, there are a number of caveats to any such investigation.

Caveat #1: One must account for the potential impact of apparently extraneous environmental contingencies on reward processing. The potential influence of such contingencies has been suggested by two recent behavioural studies (Scheres *et al.*, 2006; Solanto *et al.*, 2001). Scheres *et al.* (2006) examined temporal discounting in children (aged 6–11) and adolescents (aged 12–17) with and without ADHD. Temporal discounting (TD) refers to the decrease of subjective reward value as a function of increasing delay (Monterosso & Ainslie, 1999; Critchfield & Kollins, 2001). It may be a more sensitive measure of reward-related processes than previously used paradigms such as the Choice Delay Task, as TD functions capture the trade-off between reward magnitude and delay (Myerson *et al.*, 2001). However, TD in ADHD has received little research attention. In the TD task employed by Scheres *et al.* (2006), participants chose between small immediate rewards and

larger delayed rewards, and the size of the rewards (real money) and the delay were parametrically varied so that the subjective value of the large delayed reward could be plotted as a function of delay (a discounting function). The large reward (10 cents) was delayed by between 0 and 30 seconds (0, 5, 10, 20, and 30s), and the immediate reward varied in magnitude (0, 2, 4, 6, 8 and 10 cents). The primary hypothesis of the study was that ADHD participants would show steeper temporal discounting than controls.

Contrary to expectations, however, there were no differences between children and adolescents with ADHD and controls in temporal discounting of real monetary rewards. This result stands in contrast to previous studies that demonstrated increased preference for smaller, immediate rewards in ADHD (e.g. Sonuga-Barke *et al.*, 1992; Barkley *et al.*, 2001; Kuntsi *et al.*, 2001; Solanto *et al.*, 2001; Tripp & Alsop, 2001; Bitsakou *et al.*, 2006). Several methodological issues may account for the negative finding of this study and its divergence from previous studies which used more standard choice-delay tasks, with only one choice (e.g. 2 cents now or 10 cents after 30 seconds) repeated several times (e.g. Sonuga-Barke *et al.*, 1992; Solanto *et al.*, 2001). These issues demonstrate the crucial but perhaps subtle impact of reward and environmental contingencies on reward-related behaviour, and highlight the need to distinguish between real and hypothetical rewards and delays (e.g. Barkley *et al.*, 2001), to be cautious regarding the provision of rewards following the practice trials (as this may have increased the incentive salience of the task, an effect that was also observed by Solanto *et al.* 2001), and to be aware of the use of varying reward magnitudes and delays, which, in this study, may have decreased monotony as well as decreasing the intensity of the delay effect (Scheres *et al.*, 2006). These issues emphasise that reward-related processes and reward learning involve highly sensitive neural mechanisms, a primary function of which is to associate subtle cues in the environment with the attainment of rewards. Thus, subtle and apparently extraneous environmental and contextual factors can have considerable impact on reward-related behaviour, an important consideration which we should attempt to incorporate into our study designs.

Caveat #2: Another important consideration for neuroimaging investigations of reward-related processing in ADHD is that we sometimes may not observe a significant difference in behavioural performance between the ADHD and control groups. Nonetheless, when brain activations are examined, meaningful differences may be observed, as has been demonstrated by several studies in which the groups being compared performed at equivalent levels (e.g. Ring *et al.*, 1999; Cabeza *et al.*, 2002; Park *et al.*, 2003; Sohn *et al.*, 2004; Cannon *et al.*, 2005; Valera *et al.*, 2005). This was also the case in the neuroimaging study (discussed above), which demonstrated ventral striatal hypoactivation in individuals with ADHD during reward anticipation, despite there being no differences in behavioural performance between the ADHD and control groups (Scheres *et al.*, in press). Similarly, Ernst *et al.* (2003) showed that adults with childhood-onset ADHD had lower levels of activation than a control group in limbic areas such as the hippocampus and in the anterior cingulate during the performance of a risky decision-making task (the Iowa Gambling Task), in the absence of performance differences between the groups. These findings demonstrate that neuroimaging can provide insights inaccessible to purely behavioural analyses (Rubia, 2002).

Nonetheless, this situation represents a ‘catch-22’ situation for any neuroimaging researcher: in the absence of differences in overt behaviour, and more specifically, behavioural impairment in an ADHD group, what is the meaning of differences in brain activation? On the other hand, differences in overt behaviour may confound interpretations of differences in activation, as those activation differences may be secondary to behavioural differences such as lower accuracy rates, or slower/more variable reaction times (Murphy & Garavan, 2004). Indeed, it has been argued that activation differences between groups cannot be reliably interpreted unless the clinical and control groups are matched on performance (Callicott *et al.*, 1998).

This issue is complicated further if we are to examine neuropsychologically impaired subtypes – the selection of a subgroup within an ADHD sample who demonstrate significantly impaired performance relative to controls. If this strategy is to be employed in neuroimaging studies, and groups are mismatched on performance, we must be able to rule out potentially confounding factors such as poor motivation, lack of understanding or lack of cooperation, before differences in activation can be interpreted reliably. Another potential solution is the use of parametric designs, as these provide a within-subject comparison (control) that can aid in the interpretation of group differences in activation (Brown & Eyer, 2006).

These issues aside, careful examination of differences in activation and brain-behaviour relationships are vital to our understanding of neurobiology of ADHD. For example, Fassbender and Schweitzer (2006) recently reviewed the neuroimaging evidence for compensatory neural activations in ADHD. They suggest that the literature is consistent with an ADHD-related pattern of hypoactivity in prefrontal and midline areas of the brain and concurrently, greater recruitment or hyperactivation of more posterior visual, spatial and motor regions during task performance. However, little is known about the putative dysfunctions and compensatory mechanisms underlying these patterns of hypo- and hyperactivity, highlighting the need for considerable further research.

Caveat #3: It is also necessary to think carefully about the role of reward-related delay in ADHD. The prediction that children with ADHD would show a steeper decline in NAcc activation over the delay prior to reward seems to follow logically from the evidence suggesting that NAcc dopamine firing to future rewards is reduced in ADHD (Scheres *et al.*, in press). However, it is also possible that delay represents a ‘motivational commodity’ to ADHD children in and of itself, independent of its effects on reward salience. For instance, at the heart of the concept of Delay Aversion is the hypothesis that delay has a powerful negative salience for children with ADHD. That is, children with ADHD experience the imposition of a delay prior to receipt of rewards as punishing, and escaping the delay is negatively reinforcing. If this hypothesis is correct, then the inclusion of a delay before rewards will have two competing effects in terms of overall salience for the ADHD child: it will reduce the motivational salience (subjective magnitude) of the reward, and at the same time it will increase the salience of the delay. These responses should be dissociable on a neural level, however, as the NAcc appears to respond to positive, rewarding events, rather than to punishments (in humans, e.g. Knutson *et al.*, 2001a, but see animal studies for conflicting evidence, e.g. Schoenbaum & Setlow, 2003; Wilson & Bowman, 2005), while other areas of the striatum and the amygdala

appear to respond to both positive and negative outcomes (Delgado *et al.*, 2003; McClure *et al.*, 2004b). Nonetheless, it is important to bear in mind that both valence and salience will impact upon the functional activations observed and the inclusion of experimental manipulations to tease apart their separate influence should be considered.

11.4.3 HOW CAN WE CHARACTERISE THE DISTINCTIVE CONTRIBUTION OF 'HOT' AND 'COOL' PROCESSES AND THEIR INTERACTIONS TO ADHD

We have emphasised that interaction between 'hot' and 'cool' processing pathways is necessary for successful goal-directed behaviour, and we have suggested that Haber's (Haber *et al.*, 2000; Haber, 2003) description of the striato-nigral-striatal and thalamo-cortico-thalamic networks provides the anatomic basis through which emotion/motivation related 'hot' EF pathways influence 'cool' EF pathways. Information flow through non-reciprocal components of these spiraling circuits is unidirectional, suggesting a hierarchy of emotion/motivation affecting cognitive processing which can regulate motor outputs (Haber, 2003). Such a hierarchy may be particularly relevant to the understanding of ADHD and related disorders (Castellanos *et al.*, 2006) – as Haber points out: 'parallel circuits and integrative circuits must work together, so that the coordinated behaviours are maintained and focused (via parallel networks), but also can be modified and changed according to appropriate external and internal stimuli (via integrative networks). Indeed, both the inability to maintain and to focus in the execution of specific behaviours, as well as the inability to adapt appropriately to external and internal cues, are key deficits in basal ganglia diseases which affect these aspects of motor control, cognition and motivation' (Haber, 2003, p. 325).

Haber's description of distinct but interacting circuits prompts the examination of the loci and consequence of their interactions, and the role dysfunctional interactions might play in ADHD. A potentially crucial locus of this interaction is the anterior cingulate cortex (ACC), part of thalamo-cortical-striatal pathway (Sonuga-Barke, 2005). The ACC has been implicated in conflict-and error-monitoring processes, and more specifically, through its interconnections with PFC, in signalling the requirement for and implementing cognitive control (MacDonald *et al.*, 2000; Kerns *et al.*, 2004; Ridderinkhof *et al.*, 2004; Brown & Braver, 2005). The ACC is thus well suited to the role of integrating bottom-up reward-related signals with top-down signals in order to indicate the need for changes in behaviour and for the implementation of cognitive control. In support of this suggestion, a recent study (Cohen *et al.*, 2005) demonstrated increased connectivity between the ACC and areas implicated in reward-related processing, including the NAcc and OFC, when participants were faced with high-relative to low-risk decisions. Furthermore, a recent study (Magno *et al.*, in press) demonstrated dissociable roles for the ACC and NAcc in signalling the requirement for control and signalling response to absence of reward. Those authors suggest that the NAcc responds to primary reward-related information while the ACC uses this information in the signalling and implementation of behavioural change. There is consistent evidence for hypo-

activation of the ACC in ADHD (Bush *et al.*, 1999, Dickstein *et al.*, in press; Fassbender & Schweitzer, 2006), emphasising the requirement to investigate the ACC as a potential locus of dysfunction in the interactions between 'cool' and 'hot' EF pathways in ADHD.

A recent paper also provides other clues regarding the interactions between 'hot' and 'cool' pathways. McClure *et al.* (2004a) demonstrated that the ventral striatum, medial OPF and medial PFC showed greater activation when subjects were required to choose between small immediate and larger delayed rewards, while dlPFC, lateral OFC and parietal cortex showed greater levels of activation when participants chose the larger delayed reward over the small immediate reward. The authors suggest decision-making is governed by a competition between the more automatic appetitive processes of the ventral striatum-OFC circuit and reasoning and planning processes in fronto-parietal cortex. When the ventral striatal-OFC circuit 'wins' this competition, impatient or impulsive choice results (McClure *et al.*, 2004a).

In consideration of these findings, we suggest that an important avenue for research will be the identification and examination of potential loci of dysfunction along the 'hot' and 'cool' pathways and the neural systems for motor production with which they interact (see also Nigg & Casey, 2005). Key research questions that arise from this focus include: what is the impact of affective/'hot' processes on 'cool' EF such as decision-making? Conversely, how do 'cool' EF processes and cognitive control impact upon reward-related and motivational processes?

The potential avenues for empirical research outlined in this section may serve as the foundation for new directions in the field of ADHD research. In the next section we briefly outline what might be the focus of some of these future directions.

11.5 FUTURE DIRECTIONS

In this chapter we have outlined the evidence suggesting that decrements in 'hot' EF – reward-related and motivational processes, constitute a significant and measurable deficit in ADHD, and are distinct from deficits in other 'cool' cognitive EF processes. Pursuit of the research directions laid out in the preceding section will enable the empirical delineation of the deficits in motivational processes implicated in ADHD, and their underlying neural substrates. The development of new paradigms (Bitsakou *et al.*, 2006; Muller *et al.*, 2006) which attempt to incorporate more sensitive measures of Delay Aversion than those employed previously, is a promising step in this direction. One component of these future investigations may be the examination of 'hot' EF deficits as potential ADHD endophenotypes. The endophenotype approach has been described in detail in other chapters (Chapter 12) and in previous papers (Castellanos & Tannock, 2002). Further investigations are needed to establish whether deficits in specific 'hot' EF processes are endophenotypic for ADHD.

In highlighting the potential for examinations of 'hot' motivational processes in ADHD we have also drawn attention to a caveat – reward-related processes and reward learning involve highly sensitive neural mechanisms, a primary function of

which is to associate subtle cues in the environment with the attainment of rewards. There is thus a clear requirement that those working in the area of reward research develop an awareness of the influence of apparently extraneous environmental and contextual factors in their research.

The potential for examination of interactions between 'hot' and 'cool' EF and their underlying neural substrates represents a promising new direction for ADHD research. That ADHD individuals demonstrate hypoactivation in the ACC is an increasingly robust finding (Bush *et al.*, 1999; Dickstein *et al.*, in press; Fassbender & Schweitzer, 2006), prompting the question of how this hypoactivity might impact on the implementation of cognitive control ('cool' EF) and the interactions between 'hot' and 'cool' EF processes.

As we have emphasised throughout the chapter (see also Chapter 12), the use of neuropsychologically impaired subtypes may constitute a break-through in the characterisation of the neural substrates of ADHD (Nigg, Willcutt *et al.*, 2005). This implies the identification of a subgroup within an ADHD research sample who show a significant decrement in performance, relative to controls (e.g., as employed by Johnson *et al.*, in press). This subgroup may have a specific deficit in the neurocognitive function of interest, which is not shared by other members of the ADHD sample, but which contributes to the expression of the disorder. Comparisons between this subgroup and controls, or between this subgroup and the 'unimpaired' ADHD group, on measures of interest, should then be informative with regard to the behavioural, cognitive or neurobiological correlates of the specific deficit in the 'impaired' ADHD subgroup. The inclusion of secondary measures of impulsivity, hyperactivity, and other symptoms (e.g. questionnaires such as the Barratt Impulsiveness Scale) will aid in the examination of the potential relationships between these dissociable deficits and real-world behaviours. These steps will enable us to construct neurobiological dimensional profiles of ADHD that will improve on current symptom-based distinctions (Castellanos *et al.*, 2006). Moreover, by defining neuropsychologically impaired subgroups, the heterogeneity of a sample will be reduced, which may clarify some of the inconsistencies in behavioural findings to date. For example, a recent study observed that the preference for small immediate over larger delayed rewards demonstrated by children with ADHD was uncorrelated with the Stop Signal Reaction Time (SSRT), suggesting that inhibitory deficits and delay aversion are dissociable processes (Solanto *et al.*, 2001). Furthermore, performance on either task was only moderately associated with ADHD, but taken together, performance on both tasks correctly classified almost 90% of children with ADHD.

Once we have formed a picture of the patterns of neuropsychologically and neurologically dissociable deficits (a 'Table of Neurocognitive Elements,' something which will require considerable further research), we should be able to measure those deficits in any sample of ADHD individuals by assessing them on a battery of tasks which tap the identified span of deficits. This, in turn, may feed into the development of targeted neurorehabilitative interventions (see Chapter 21). Without demonstrable (significant) impairment on a given cognitive ability, cognitive remediation techniques aimed at that ability would fail to show significant improvement across an ADHD sample, as a subset of that sample will not have been impaired on that function in the first place. Thus the establishment of neuro-

psychological subtypes of ADHD is a critical step in moving the field of research forward, both in terms of basic research, and in terms of the design of rehabilitative interventions.

Finally, the DA reward prediction system, and in particular the ventral striatum and NAcc, is central to the understanding of substance abuse and addiction. Drugs such as opiates, nicotine, cocaine and amphetamine increase DA concentration by either increasing its release or blocking its reuptake (Schultz, 2001). Work with animal models suggests that DA neurons in the ventral striatum respond to these drugs in a similar way to natural rewards. Thus natural reward and drug-seeking behaviour might share a common path in the influence of the reward message on goal-directed behaviour (Schultz, 2001). Increasing knowledge about neurophysiological reward mechanisms may therefore help provide us with a better understanding of the mechanism of action of addictive drugs. This possibility is of great relevance to the study of ADHD, as we know that individuals with a diagnosis of ADHD are more susceptible to substance abuse than the general population (e.g. Biederman *et al.*, 1995; Biederman *et al.*, 1999). Substance abuse in ADHD has been interpreted by some as self-medication, and it has been suggested that treatment with psychostimulants may decrease the risk for substance abuse in ADHD (Wilens, 2004). The link between the dysfunctional reward processing mechanisms and the development of substance abuse disorder represents an important new frontier in ADHD research.

11.6 SUMMARY

In this chapter we have provided an outline of some of the main avenues of investigation, and potential research hypotheses, in the examination of reward and motivational processes in ADHD. We have emphasised that the heterogeneity intrinsic to the disorder demands a multi-faceted approach, one which bridges the key areas of ADHD research, particularly those that examine dysfunction in 'cool' EF and those that examine deficits in reward-related and other motivational processes ('hot' EF). In addition, we have emphasised the need to examine the potential foci of interaction between these distinct but intertwined processing pathways. It is in this way that we believe the field will move forward to provide a deeper understanding of the etiological processes underlying ADHD, and provide targets for neurocognitive interventions.

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