specify these changes. Additionally, future work will have to assess the apparent specificity of these long term microstructural changes to the nigrostriatal but not mesolimbic SN/VTA. Due to the high level of heterogeneity in pharmacological responses in these regions (Browder et al. 1981; Ashby et al. 2000; Goldstein & Litwin 1988; Gervais & Rouillard 2000; Mejías-Aponte et al. 2009; Mereu et al. 1987; Klink et al. 2001), numerous mechanisms could account for this. Further animal work will be required to disentangle how stimulant medication exerts these selective long-term effects.

5 Disorder-specific effects of psychostimulants on reward and novelty computation in ADHD

A comprehensive theoretical model of ADHD needs to account for impaired reward-related behavior and its amelioration by stimulant medication. Computational models of reinforcement-learning have helped dissect discrete components of reward-related function. Novel options, even when unrelated to choice outcome, bias decision-making as if possessing intrinsic reward value to guide decisions toward uncertain options. Individuals with ADHD show heightened novelty-seeking personality traits, yet how this influences reinforcement-learning or is improved by medication, is currently uncertain. Here I use a reinforcement-learning task during fMRI to model effects of novelty on reward-related behavior in 30 adults with ADHD and 30 healthy participants. Both groups were tested twice (on and off stimulant medication) to examine therapeutic effects. ADHD patients showed impaired task performance as resulting from a greater tendency to pick novel options, itself associated with heightened novelty processing within the substantia nigra/ventral tegmental area (SN/VTA). These deficits were rescued by stimulant medication in a disorder-specific manner. Specifically, in ADHD medication reduced selection of non-rewarding novel items and normalized reinforcement-learning deficits. This improved performance was also associated with reduced neural responses to novelty within SN/VTA. In contrast, stimulant medication amplified SN/VTA responses to novelty and impaired reinforcement-learning in controls. In addition, aberrant novelty valuation was normalized during long-term stimulant treatment: patients taking medication for longer exhibited significantly lower novelty bonus and decreased SN/VTA reactivity to novelty. Together these findings provide a neurocomputational account of how aberrant novelty processing biases reward-related choice and acts as a disorder-specific target for the pharmacological management of ADHD symptoms.

5.1 Introduction

Impaired reward learning in ADHD (Frank et al. 2007; Thoma et al. 2015) has been theorized to play a central role in both the symptomatic expression and aetiology of the disorder (Luman et al. 2010). Temporal difference (TD) learning models may play an important role in clarifying the nature of these abnormalities. TD models are a computational approach to reinforcement learning, addressing how sources of reward are accurately determined by an agent in a constantly updating environment. This occurs through an iterative error-driven learning, that is described more fully in Chapter 1.

Over the past decade these TD learning models have allowed computation of 'hidden' learning signals and quantification of learning from reward *in vivo* and have also provided a powerful method for characterizing human reward-related behavior (Steinberg et al. 2013). Through calculation of trial-by-trial prediction error signals TD models have demonstrated a tight coupling between reward-related learning signals and dopaminergic neuronal activity (Schultz et al. 1997; Hollerman & Schultz 1998) within the substantia nigra/ventral tegmental area (SN/VTA) and ventral striatum (Bayer & Glimcher 2005; Montague et al. 1996; O'Doherty et al. 2003; McClure et al. 2003; Waelti et al. 2001). This approach has helped clarify mechanisms of impaired reward-related processing in other disorders characterized by dopaminergic dysfunction including Schizophrenia and Parkinson's disease (Rutledge et al. 2009; Murray et al. 2008). More broadly, TD models also present a theoretical framework for characterizing the behavioral impact of other salient influences, such as stimulus novelty, on reward-related decision-making processes and their instantiation within the brain (Wittmann et al. 2008). Importantly however, there is as yet no precise account of how reinforcement-learning to reward is altered in ADHD, nor how this is ameliorated by stimulant medication (Frank et al. 2007; Thoma et al. 2015; Luman et al. 2010).

As outlined in Chapter 1, reduced learning rates in TD models (i.e. slower updating of reward values with experience) are associated with reduced dopamine levels (Rutledge et al. 2009), and may therefore mediate the association between impulsive reward seeking and hypodopaminergia in ADHD (Williams & Dayan 2005). Such an account may also help explain the efficacy of stimulant medication in improving reward-learning in ADHD (Frank et al. 2007; Thoma et al. 2015), since dopaminergic medications enhance reward-related learning rates in Parkinson's disease (Rutledge et al. 2009).

Another pressing issue highlighted in Chapter 1 that has yet to be explored in ADHD is the role of aberrant novelty signaling in the disorder. Stimulus novelty is a potent trigger for the activation of dopaminergic neurons within SN/VTA (Schultz 1998). This mechanism can bias preference towards novel options and drive exploratory behavior (Wittmann et al. 2008; Kakade & Dayan 2002). Novelty preference is highly adaptive, enabling the identification of new sources of potential reward and reducing the uncertainty evoked by unfamiliar stimuli. However, novelty preference also entails risk. Aberrantly high novelty valuation is linked to significant personal harm, including development of substance abuse (Wills et al. 1994). It is noteworthy that heightened novelty seeking is robustly observed in ADHD (Downey et al. 1997; Lynn et al. 2005; Jacob et al. 2014), and ADHD populations appear to be at higher risk of clinical problems associated with these traits, such as substance use disorders (Harpin 2005). Furthermore, novelty-seeking personality traits (Kluger et al. 2002; Munafò et al. 2008; Roussos et al. 2009; Ekelund et al. 1999; Tomitaka et al. 1999; Strobel et al. 1999; Okuyama et al. 2000; Ebstein et al. 1996) and ADHD (LaHoste et al. 1996; Rowe et al. 1998; Smalley et al. 1998; Faraone et al. 1999; Faraone et al. 2001; Barr et al. 2000; Eisenberg et al. 2000) share genetic correlates in dopamine receptor (particularly DRD4) polymorphisms. These genetic differences may play an important role in the development of inattentive phenotypes (Lasky-Su et al. 2008; Gizer & Waldman 2012), as they appears to influence attention processing even in infancy (Auerbach et al. 2001). However, to date no work has specifically examined how increased novelty-seeking impacts reward learning in ADHD.

TD models may again be able to help address this. Computational accounts of reward learning propose that novelty encourages exploratory behavior through a fictive 'bonus' signal that enhances the reward value of novel stimuli (Kakade & Dayan 2002). Supporting this, both novelty bonus and reward prediction error signals are associated with phasic dopaminergic activity in mesolimbic reward pathways (Steinfels et al. 1983; Ljungberg et al. 1992; Horvitz et al. 1997; Schiemann et al. 2012; Kakade & Dayan 2002; Wittmann et al. 2008; Bunzeck & Düzel 2006; Zald et al. 2008). Correspondingly, increased novelty bonus signals are also observed in patients with impulse control disorders associated with Parkinson's disease (Djamshidian et al. 2011). It appears possible that similar changes underpin the impairments in impulse control that are characteristic of ADHD, yet this is currently unknown. Furthermore, it remains unclear why stimulant medications improve hyperactive/impulsive symptoms in ADHD, given

the expectation that they may heighten novelty associated 'bonus' signals and potentially exacerbate these symptoms.

To address these questions, I tested thirty ADHD patients and thirty matched controls on a reinforcement-learning task shown to be sensitive to effects of stimulus novelty on reward-related behavior. Each participant completed the task during fMRI on two separate occasions, once after taking stimulant medication and the other after placebo administration, in a randomized double-blinded study.

5.2 Methods

5.2.1 Participants

The same cohort of 30 adults with ADHD and 30 matched controls were used as in previous chapters.

5.2.2 Study design

As described previously, a randomized, repeated-measures, double-blind, placebo-controlled study design was used in which all participants attended two experimental sessions separated by a minimum of 1 week. See Chapter 2 for further details on dosing and timings.

5.2.3 Reinforcement learning task with novelty manipulation

After drug administration, participants were immediately familiarized with 32 grey-scale landscape images (Bunzeck & Düzel 2006) over a fifteen minute session. This timing was important to ensure equivalent encoding (familiarization) across drug and placebo conditions. The computerized familiarization session consisted of two components: (i) A passive viewing component, where they were exposed to each of the 32 pictures 4 times in a random sequence, and (ii) an active familiarization paradigm where they were asked whether each picture had a building in it, with each picture again presented four times.

Ninety minutes after drug dosing, participants completed an MRI session (75 minutes duration), including three runs of the reinforcement-learning task (three-armed bandit task) encompassing a novelty manipulation (Wittmann et al. 2008; Djamshidian et al. 2011) (Figure 5.1). Task performance was timed to coincide with peak dopamine transporter occupancy of the drug (Volkow et al. 1998). Each run lasted thirteen minutes and contained eighty consecutive trials, each consisting of three options represented by grey-scale landscape images (Wittmann et al. 2008).

Each trial the participant was presented with three options, each of which had a fixed random probability (mean: 33%) of winning a £1 reward. Participants were instructed to choose options that maximized their total reward wins, and they were informed that reimbursement would be proportional to overall task performance. As participants did not have any prior knowledge of the value (ie probability of winning) of each option, to maximize reward they were forced to learn the value of options by selecting them over several trials. Between each trial, options were randomly spatially rearranged to ensure that participants were responding to the option (ie the image) rather than the position.

On 25% of trials, an existing option was randomly replaced by a new one. Half of the newly introduced images were novel (previously unseen during the familiarization component of the task detailed above) and half were familiar (previously seen during the initial familiarization phase) (Figure 5.1) (Panel iii). Critically, while each picture differed in its reward value, the 32 image sets of novel and familiar stimuli were balanced to have the same reward probability distributions (mean 33%). This allowed measurement of participants' subjective valuation of novel and familiar stimuli that are otherwise identical in expected value.

Alternate versions of the task (with non-overlapping stimulus sets) were used for each testing session (randomized across participants) to maintain the novelty manipulation. No significant differences in reward or behavioural performance were observed between the two alternative versions of the task (all $p > 0.05$). In each trial, participants were given 3.5s to select an option on each trial, after which their choice was highlighted with a grey border (3s) before feedback (1.5s) in the form of a '£1' or '£0' sign as superimposed on the chosen stimulus (Figure 5.1). If participants failed to respond in time, 'No response' was displayed on the screen for 4.5s. A fixation cross was displayed between each trial for 1-3.5s.

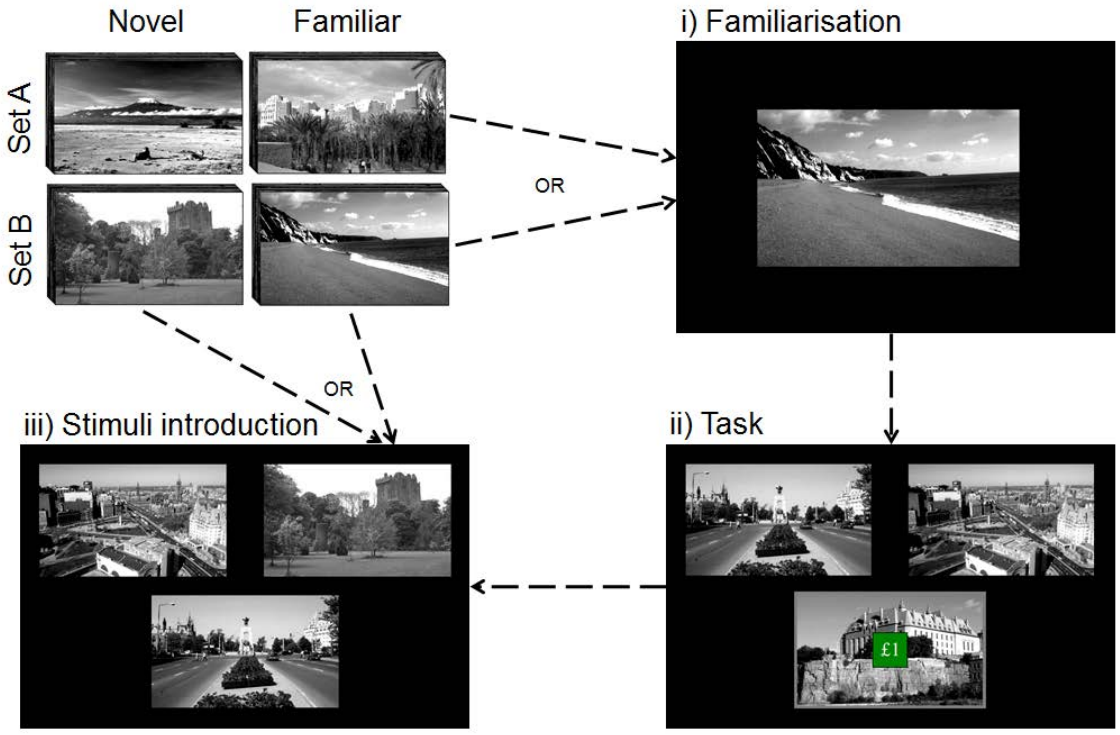

Figure 5.1 Novelty processing task.

A set of 64 pictures (A or B top left) was randomly allocated for each session. i) Participants were familiarized to half of the pictures by passive viewing then answering whether the picture contained a building. ii) During fMRI participants performed a three-armed bandit task, choosing between three options on each trial. Each option was represented as an image and had a fixed probability of reward. Each trial consists of stimulus presentation, choice feedback, and reward feedback. This is followed by a jittered inter-trial period in which a fixation cross is presented. After each trial, option locations are randomly shuffled. (iii) On 25% of trials at a fixed period an option is randomly replaced by a new one from either the familiar or novel subset.

5.2.4 Computational modeling of choice behavior

We characterized each participant's trial-to-trial choices using a temporal-difference learning model with four free parameters as it Wittmann et al. (Wittmann et al. 2008): α learning rate, β inverse temperature or choice randomness, and Q_f and Q_n, the initial values of familiar and novel stimuli respectively. Initial values of each picture were set to Q_f if the picture had been pre-exposed during the familiarization phase, and to Q_n if not. Values for the chosen option (*Q*) were updated according to the delta (δ) rule:

$$Q(c, t+1) = Q(c, t) + \alpha \bullet \delta(t)$$

Where δ denotes the reward (r) prediction error:

$$\delta(t) = r(t) - Q(c, t)$$

The probability of choosing an option was modeled according to a softmax selection strategy, where the probability of choosing an option *c* (out of the 3 options *k*) on trial *t* is:

$$P(c, t) = \frac{exp(\beta \bullet Q(c, t))}{\sum_{k=1}^{3} exp(\beta \bullet Q(k, t))}$$

Model parameters were optimized on a per-subject, per-session basis to minimize the negative log-likelihood of the observed sequence of choices. Model fit did not differ between ADHD and control groups. Novelty bonus was calculated as Q_n-Q_f, with a positive value reflecting a preference for novel over familiar options.

Model-based regressors were generated for analysis of the neuroimaging data by entering each participant's actual sequence of rewards and choices within the learning model to produce per-subject, per-trial estimates of the values Q(c,t) and error signals δ(t).

To study effects of pharmacological manipulation and ADHD diagnosis on novelty processing specifically, following Wittman et al.(Wittmann et al. 2008), I repeated these simulations using a second model where the initial value of novel and familiar stimuli were set to be equal i.e. Q_n=Q_f. This generated a second sequence of values

$Q_{base}(c,t)$ and prediction errors $\delta_{base}(t)$, representing baseline values *without* the additional effect of novelty. By comparing these two models, I calculated the additive value $Q_{add}(c,t) = (Q(c,t) - Q_{base}(c,t))$ and prediction error $\delta_{add}(t) = \delta(c,t) - \delta_{base}(t)$ associated with stimulus-novelty. Primary behavioral outcome measures included the four free model parameters, i.e. α learning rates, β inverse-temperature, initial stimulus valuations Q_n and Q_f. To study novelty specifically, I examined novelty bonus (Q_n-Q_f), tendency to pick novel options on their first presentation, and the number of consecutive trials in which the novel object was selected.

5.2.5 Magnetic Resonance Imaging (MRI)

T2*-weighted echo planar images (EPIs) were acquired on a 1.5T Siemens Avanto MR scanner equipped with a 32 channel head-coil using a -30° tilted acquisition to reduce orbitofrontal dropout (Deichmann et al. 2003). Each volume provided whole brain coverage (34 interleaved ascending 3mm axial slices with 1mm inter-slice gap, echo-time 43msec: TR 2.52s, in-plane resolution 3mm). Multi-parameter mapping using three co-localized 3D multi-echo flash sequences (See Chapters 2 and 3 for further details) was additionally acquired to provide high-resolution magnetization transfer (MT) saturation images with high contrast for sub-cortical regions of interest (Helms et al. 2009). MT images were segmented then normalized in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) to aid group level anatomical localization. Diffusion weighted MRI and multi-echo resting state EPI datasets were also acquired, though are not reported here.

EPIs were analyzed in an event-related manner in SPM8: Pre-processing consisted of spatial realignment, segmentation and normalization of the mean EPI image to a standard EPI template then spatial smoothing with an 8mm FWHM Gaussian kernel. Subject-specific realignment parameters were modeled as covariates of no interest to correct for motion artifacts. Stimulus and outcome onsets were modeled as separate delta functions and convolved with a canonical hemodynamic response function and its temporal derivative. Computationally determined prediction errors ($\delta_{base}(t)$ and $\delta_{add}(t)$) and Q-values ($Q_{base}(c,t)$ and $Q_{add}(c,t)$), were used as additional regressors that parametrically modulated outcome and cue onsets respectively. Linear contrasts of regression coefficients were computed at the individual subject level then taken to group level mixed measures ANOVA (repeated factor: (drug, placebo), between-

subject factor: group (ADHD, control)) to assess critical group x condition interactions for $\boldsymbol{\delta}_{base}(t)$ and the novelty signal ($Q_{add}(c,t)$ and $\boldsymbol{\delta}_{add}(t)$).

5.2.6 A priori regions-of-interest

Bilateral ventral striatum and the substantia nigra/ventral tegmental area (SN/VTA) were each defined as *a priori* regions-of-interest (ROI), based on published findings of Wittmann et al. using this task.(Wittmann et al. 2008) The ventral striatum region was defined using the mask of Martinez et al. (Martinez et al. 2003) and included the nucleus accumbens, ventral caudate rostral to the anterior commissure (AC), and the ventral putamen rostral to the AC. The SN/VTA was manually traced from the mean normalized template of all participants' MT saturation maps (Düzel et al. 2008). Results are reported for clusters surviving stringent Family-Wise-Error (FWE) $p<0.05$ correction for the whole brain or appropriate ROI.

5.2.7 Questionnaires

The Conner's self-report Adult ADHD Rating Scale (CAARS) (Conners et al. 1999) was used to index current ADHD symptom severity and the Tridimensional Personality Questionnaire (TPQ) (Cloninger et al. 1991) to measure trait novelty-seeking. Beck's Depression Inventory (BDI) (Beck et al. 1996) and the State and Trait Anxiety Inventory (STAI) (Spielberger 1983) were used to assess depression and anxiety scores respectively. The Multidimensional Personality Questionnaire (MPQ) was also administered (Tellegen & Waller 2008) for use in a separate study. Behavioral analyses were performed in SPSS using mixed-measures ANOVAs followed by post-hoc t-tests. Spearman's *rho* was used to assess relationships between behavioral measures.

5.3 Results

5.3.1 Novelty seeking personality traits

Consistent with larger population studies (Downey et al. 1997; Lynn et al. 2005; Jacob et al. 2014), ADHD participants scored significantly higher on novelty-seeking and

harm-avoidance factors of the TPQ (Novelty-seeking: ADHD=22.9±4.8, controls=17.6±5.6, $F_{(1,57)}$=15.29, p<0.001, Harm-avoidance: ADHD=17.1±7.5, controls=11.9±7.5, $F_{(1,57)}$=15.29, p=0.01), but not reward-dependence (ADHD=13.0 ±4.0, controls=12.3±3.8, $F_{(1,57)}$=0.55, p=0.46) or persistence (ADHD=5.3 ±2.3, controls=4.6±2.0, $F_{(1,56)}$=1.38, p=0.245).

5.3.2 Behavioral Responses

Stimulant medication had strikingly different effects on the performance of participants with ADHD, compared to controls. Specifically, stimulant medication enhanced the performance of ADHD participants (amount won on task, mean±SE: stimulant: £90.5±1.85; placebo £86.3±1.76), yet impaired the performance of controls (stimulant: £87.6±1.52; placebo: £91.8±1.80; Drug x Group: $F_{(1,58)}$=6.95, p=0.011; Group: $F_{(1,58)}$=0.59, p=0.445; Drug: $F_{(1,58)}$<0.01, p=0.988)). This effect remained significant after controlling for differences in mood (BDI) or trait anxiety (STAI) (p=0.019). Post-hoc comparisons revealed that unmedicated patients showed impaired performance compared to controls on placebo ($F_{(1,58)}$=5.17, p=0.027).

To investigate these behavioural differences in more detail, this work first tested for effects on individual parameters of the behavioural model. Similar to effects observed in task performance, stimulant medication had dissociable effects on learning rates in the ADHD and control groups (Drug x Group: $F_{(1,58)}$=4.17, p=0.046) with no main effect for drug ($F_{(1,58)}$=0.03, p=0.873) or group ($F_{(1,58)}$=1.27, p=0.264) independently. Stimulant medication increased basal learning rates in ADHD (mean±SE, stimulant: 0.48±0.06; placebo: 0.39±0.04), but had the opposite effect in controls (stimulant: 0.46±0.06; placebo: 0.54 ± 0.05). Post-hoc comparisons revealed that unmedicated ADHD was associated with lower learning rates than controls ($F_{(1,58)}$=4.93, p=0.030). Although this interaction only met trendwise significance (p = 0.110) after correction for BDI and STAI scores, neither BDI or STAI scores predicted baseline learning rates (BDI: r = 0.21, p = 0.262; STAI: r = -0.11, p = 0.560). Choice-randomness (β) did not significantly differ (Drug: $F_{(1,58)}$=0.28, p=0.598; Group: $F_{(1,58)}$=0.12, p=0.730; Drug x Group: $F_{(1,58)}$=0.06, p=0.803; ADHD: stimulant: 7.18±1.54; placebo: 7.58±2.06; Controls: stimulant: 7.58±1.27; placebo: 8.69±2.29).

Table 5.1 Behavioural Data and Model parameter estimates in ADHD and controls

Measure	ADHD		Controls	
	Drug	Placebo	Drug	Placebo
Amount won (£)	90.5 (1.85)	86.3 (1.76)	87.6 (1.80)	91.8 (1.80)
Novel options picked on first presentation (%)	16.8 (1.40)	17.2 (1.46)	12.3 (0.96)	12.3 (1.08)
Familiar options picked on first presentation (%)	14.8 (1.32)	16.5 (1.20)	15.0 (1.30)	13.0 (14.0)
Persistence in picking optimal novel options	4.5 (0.27)	3.9 (0.19)	4.12 (0.13)	4.24 (0.11)
Persistence in picking non-optimal novel options	3.2 (0.28)	3.8 (0.31)	3.77 (0.29)	3.64 (0.25)
Persistence in picking non-optimal familiar options	4.6 (0.35)	4.7 (0.15)	4.5 (0.21)	4.8 (0.19)
Persistence in picking non-optimal familiar options	3.6 (0.19)	3.6 (0.21)	3.6 (0.24)	3.4 (0.27)
Qn	0.62 (0.06)	0.57 (0.07)	0.53 (0.05)	0.46 (0.05)
Qf	0.56 (0.06)	0.52 (0.06)	0.49 (0.05)	0.45 (0.06)
α	0.48 (0.06)	0.39 (0.04)	0.46 (0.06)	0.54 (0.05)
β	7.18 (1.54)	7.58 (2.06)	7.58 (1.27)	8.69 (2.29)

Amount won: Cumulative amount won over the course of the task; *Novel/familiar options picked on first presentation (%):* The percentage of novel/familiar options that are selected on their first presentation within the paradigm; *Persistence in picking optimal/non-optimal novel/familiar options:* The number of times a familiar/novel option was conseculatively selected after it was first introduced and selected. Optimal/non-optimal refers to whether the option being selected was the most valuable of the options present at that point. *Qf & Qn:* The initial values of familiar and novel stimuli respectively; *α:* the learning rate; *β:* the inverse temperature parameter.

Across groups, participants showed a preference for novel compared to familiar stimuli: novelty bonus = £0.039±0.01; $F_{(1,58)}$=10.84, p<0.005). ADHD participants expressed a novelty bonus more than double that observed in controls (£0.054±0.018 versus £0.024±0.015). ADHD participants were also significantly more likely than controls (Group x Familiarity: $F_{(1,58)}$=8.83, p=0.030) to choose novel than familiar options on their first presentation (% novel items selected on first presentation: ADHD: 16.8±1.23; Control: 12.3±0.09, $F_{(1,58)}$=8.83, p=0.004), % familiar items selected on first presentation: ADHD: 15.3±1.03; Control: 14.0±1.05; $F_{(1,58)}$=0.72, p=0.399), indicating a heightened salience of intrinsically 'novel' stimuli in the ADHD group rather than an increased propensity to choose all newly introduced stimuli. Whilst only a trend remained (Group x Familiarity; p = 0.078) for the interaction after controlling for depression and anxiety, again, neither score was associated with the tendency to pick novel (BDI: r = -0.14, p = 0.471; STAI: r = 0.05, p = 0.801) or familiar stimuli (BDI: r = -0.24, p = 0.210; STAI: r = -0.12, p = 0.523).

5.3.3 Relating novelty responses to drug-induced enhancement of task performance

We further investigated the relationship between novelty and task performance, by testing whether differences in ADHD participants' responses to novel vs familiar stimuli underpinned inter-individual differences in drug-related enhancement of performance on the task ([money (£) won on stimulant - money won on placebo]/ money won on placebo). As anticipated, better performance on medication was associated with a lower (i.e. more accurate) initial valuation of both novel (Qn) and familiar (Qf) stimuli (both *rho* = -0.53, p = 0.009; Table 5.1). However, *persistence* in selecting novel and familiar stimuli after their initial introduction differentially predicted performance on the task. Specifically, poorer un-medicated performance was associated with a greater persistence in selecting novel stimuli after their initial introduction (*rho* = -0.41, p = 0.025) and a trend towards lower persistence in selecting familiar options (*rho* = 0.36, p = 0.055). This baseline preference for novel options additionally predicted greater performance enhancement on stimulant medication (*rho* = 0.46, p = 0.011).

As the additive novelty bonus decays as a product of the learning rate, the increased learning rates observed in medicated patients resulted in a steeper decay of novelty valuation. Consequently on medication, valuation biases of novel stimuli were reduced

over fewer trials, potentially allowing more accurate discrimination of high and low value novel options. To test this, I examined the number of consecutive trials in which participants chose novel options when they were optimal (i.e. when the novel option had the greatest value out of the available choices) or non-optimal (i.e. when the novel option was not of greatest value).

Overall, participants showed a greater tendency to persist with optimal options rather than non-optimal ones ($F_{(1,58)}$=10.04, p=0.002). Medication ($F_{(1,58)}$<.01, p=0.970) or group status ($F_{(1,58)}$=0.32, p=0.572) did not have any general effects on choice persistence. However, medication did differentially effect how long participants selected optimal and non-optimal choices in each group (Drug x Optimality x Group: $F_{(1,58)}$=4.80, p=0.032; Figure 5.2B). In patients with ADHD, medication selectively *enhanced* persistence towards optimal novel options (Drug: 4.5±0.27; trials Placebo: 3.9±0.19 trials), and *reduced* persistence for non-optimal options (Drug: 3.2±0.28 trials; Placebo: 3.8±0.31 trials) (Drug x Optimality: $F_{(1, 28)}$=7.60, p=0.010). This pattern of effects was not observed in the control group (Optimal trials: Drug: 4.1±0.13 trials; Placebo: 4.2±0.11 trials; Non-optimal trials: Drug: 3.8±0.29 trials; Placebo: 3.6±0.25 trials; Drug x Optimality $F_{(1,28)}$=0.25, p=0.624). Furthermore, this shift towards more optimal choices was not observed for familiar stimuli ($F_{(1, 58)}$=0.10, p=0.756), indicating that stimulant medication selectively enhanced ADHD participants' performance by inducing a steeper decay in the additive value of novelty. This subsequently optimized decisions directed at both familiar and non-familiar stimuli. Again, only a trend remained for the (Group x Drug x Optimality; p = 0.082) interaction after controlling for depression and anxiety, though neither score was associated with the tendency to pick optimal (BDI: r = 0.10, p = 0.592; STAI: r = 0.07, p = 0.592) or non-optimal options for longer (BDI: r = 0.15, p = 0.437; STAI: r = -0.21, p = 0.261).

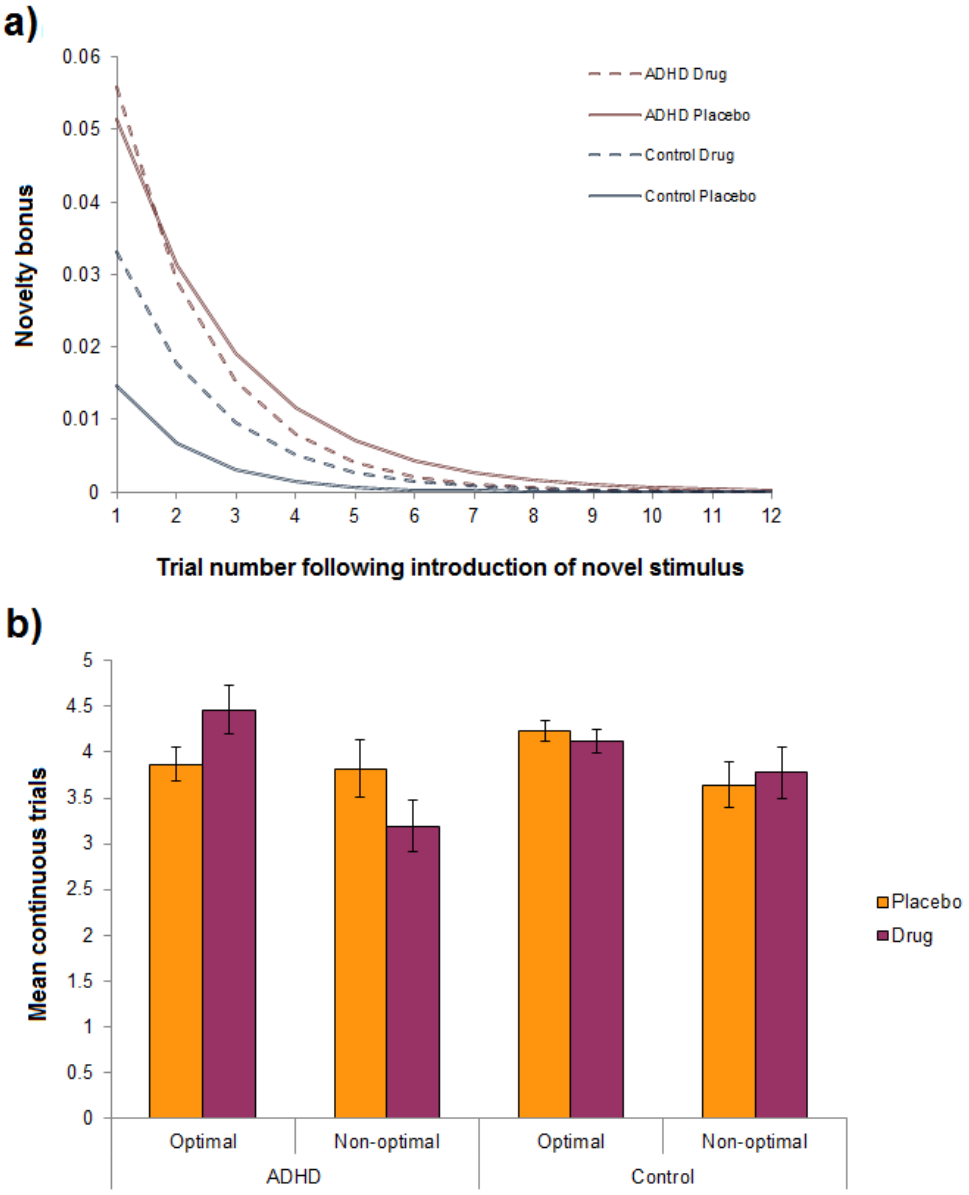

Figure 5.2 Novelty bonus decay and novelty-directed choice optimality

(a) The effect of learning rate on decay of the novelty signal within different conditions. As a novel stimuli is familiarised over a series of trials it decays according to the learning rate (α). Enhanced learning rates in the ADHD condition results in a steeper decline of the additional value attributed towards a novel stimulus. Despite starting marginally higher, the effect of this increased decay means that this novelty bias is actually lower in the drug condition by the second presentation (Drug: 0.029; Placebo: 0.031). (b) Pattern of effects of stimulant medication on optimal vs non optimal choices. In ADHD, medication significantly reduced the length of time spent choosing a newly introduced novel option that was low valued, whilst enhancing time spent picking novel options if it was high valued.

5.3.4 Effects of treatment duration on responses to novelty

Despite having a mean novelty bonus more than double that of controls, ADHD patients showed marked inter-individual differences that overshadowed the statistical significance of group effects ($F_{(1,58)}$=1.59, p=0.213). Previous studies show long-term alterations in striatal dopamine availability following sustained methylphenidate use (Volkov et al., 2012). The present study therefore investigated whether, in the ADHD group, individual differences in novelty bonus related to duration of stimulant medication treatment. Strikingly, this analysis demonstrated a significant negative correlation between treatment duration and baseline novelty bonus (*rho*=-0.44, p=0.018; after additionally controlling for BDI and STAI *rho* = -0.43, p = 0.036), i.e. patients treated the longest showed the lowest novel bonuses.

5.3.5 Striatal and SN/VTA reward and novelty signals

Consistent with earlier reports (McClure et al. 2003; O'Doherty et al. 2003; Pessiglione et al. 2006), computationally determined reward prediction error (δ_{base}) showed a tight correlation (whole brain FWE p<0.001), with bilateral ventral striatum and orbitofrontal cortex activity, and in several other frontal and parietal regions across groups (Figure 5.3; Table 5.2). In addition, this data also revealed a significant Group x Drug interaction for δ_{base} within the left ventral striatum (SVC: p = 0.021; after correction for BDI and STAI, SVC: p = 0.027), where the ADHD group exhibited a significant reduction in neural signals encoding reward prediction error while on stimulant medication compared to placebo. The opposite pattern was observed in controls (Figure 5.4a).

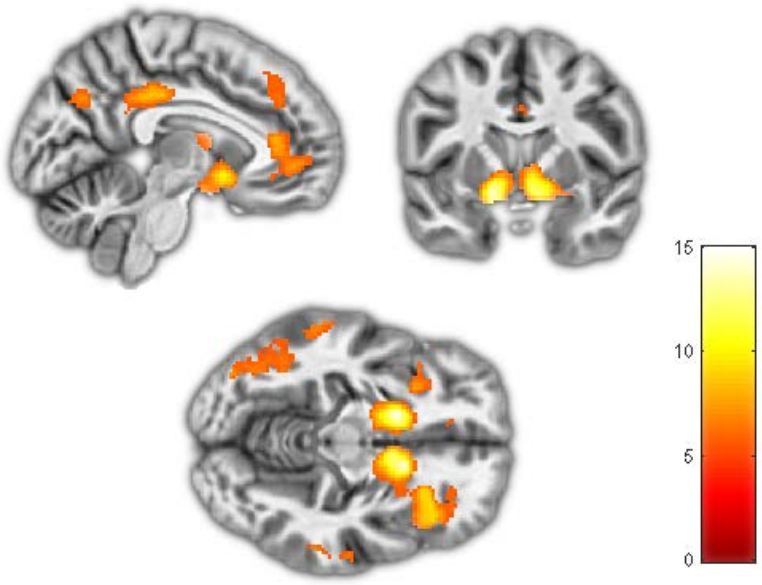

Figure 5.3 Main effect of δ_{base} with prominent activations in the ventral striatum. Thresholded at $p_{FWE} < 0.05$

Table 5.2: Main effect of reward prediction error (δ_{base})

Side	Region	Peak Coordinates	Z	*K (cluster)*	*FWE p*
L	Ventral striatum	[-12 8 -12]	>8	539	<0.001
R	Ventral striatum	[14 12 -10]	>8	733	<0.001
L	SN/VTA	[-8 -24 -14]	3.29	2	(0.02)
R	SN/VTA	[8 -14 -12]	3.56	13	(0.007)
L	Inferior frontal, orbitalis	[-30 22 6]	6.71	186	<0.001
R	Inferior frontal, orbitalis	[35 25 -10]	7.30	570	<0.001
L/R	PCC	[0 -28 38]	>8	1333	<0.001
L	Inferior parietal	[-54 44 48]	>8	1845	<0.001
R	Inferior parietal	[52 -56 32]	6.46	473	<0.001
L/R	Medial prefrontal	[4 40 16]	7.37	1249	<0.001
L	Middle temporal	[-58 -42 0]	7.29	832	<0.001
R	Middle temporal	[62 -38 -2]	6.63	274	<0.001
L	Superior frontal	[12 46 46]	6.75	219	<0.001
R	Superior frontal	[-14 36 48]	6.94	552	<0.001
L	Insula	[-38 0 6]	5.55	34	<0.001
R	Insula	[40 2 4]	6.62	90	<0.001
R	Cerebellum	[36 -70 -38]	6.48	83	<0.001
L	Precuneus	[-4 -68 34]	6.25	83	<0.001
L	Pars Orbitalis/triangularis	[-48 38 0]	6.12	211	<0.001
L	Pars triangularis	[-52 12 14]	6.00	83	<0.001
L/R	Thalamus	[8 -2 14]	5.87	219	<0.001
L	Middle frontal	[-40 12 44]	5.83	72	<0.001
R	Pars triangularis	[54 24 16]	5.30	33	<0.001

Across conditions, a corresponding correlation with novelty prediction error was not observed at the stringent thresholds employed here. However, complementing the findings for reward prediction error, a significant group x drug interaction in the SN/VTA was observed (whole-brain cluster *FWE p* = 0.027; After correction for BDI and STAI: *FWE p* = 0.036) indicating a significant reduction of novelty-related prediction error in ADHD participants on stimulant medication compared to placebo, and a converse pattern observed in controls (Figure 5.4b). Corresponding to the reduction in behavioural novelty bonus observed in patients who had been on medication longer, activity within this cluster correlated negatively with time on medication (SVC: *FWE p*=0.003).

Finally, I sought to investigate whether drug-related reductions in baseline ventral striatal prediction error signaling or SN/VTA novelty processing best explained the drug-induced enhancement of performance in ADHD. Consonant with the behavioural findings, drug-induced reductions in SN/VTA novelty-related prediction error (*rho* = -0.45, *p* = 0.037) but not ventral striatal reward prediction error signaling (*rho* = 0.04, *p* = 0.873) was related to improved reward learning. Of note these findings, survived correction for age, total brain volume and anxious and depressive symptomatology.

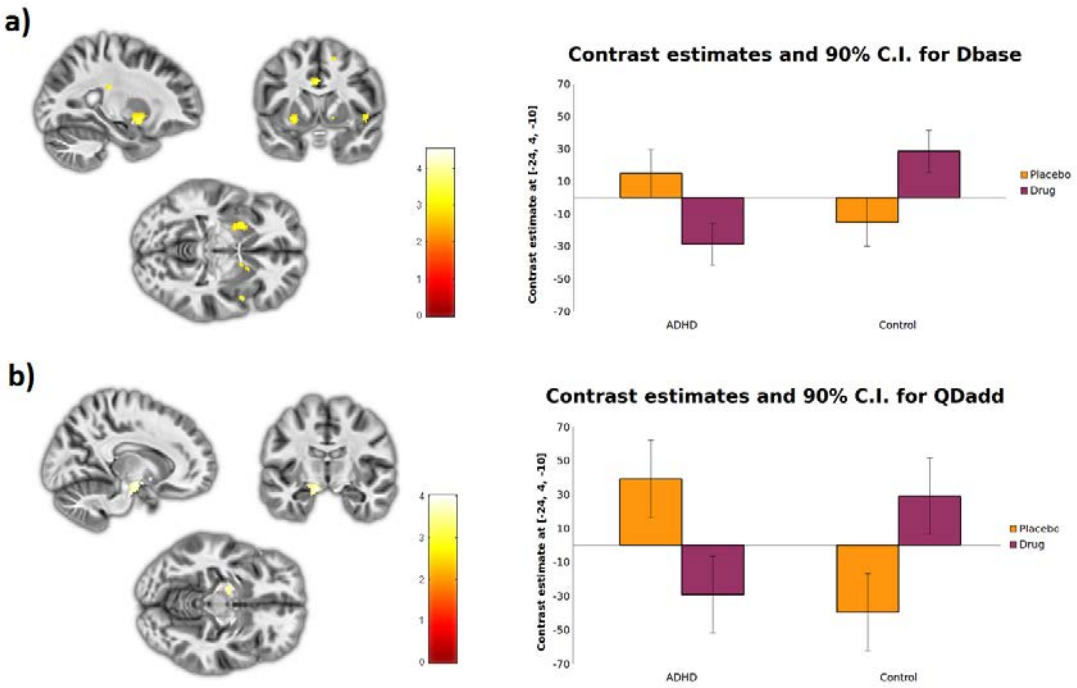

Figure 5.4 Group x Drug interactions for δ_{base} and novelty signaling.

(a) Group x Drug interaction of δ_{base} in the ventral striatum. Thresholded at $p_{unc} < 0.005$ for display purposes. (b) Group x Drug interaction of δ_{base} in the substantia nigra/ventral tegmental area. Thresholded at $p_{unc} < 0.001$.

5.4 Discussion

These results provide evidence of impaired reward learning in ADHD and demonstrate attenuation of this deficit by stimulant medication. Furthermore, they identify specific neuro-computational mechanisms underpinning these abnormalities. Specifically, ADHD participants were characterized by both greater reinforcing value of novelty ('novelty bonus') that was linked to heightened phasic signaling in the SN/VTA, and a reduction in the rate of value-updating in response to reward (lower learning rate). This heightened valuation of novelty, coupled with a slower decay in its rewarding properties, served to bias ADHD patients to repeatedly select novel options at the cost of choosing familiar, potentially more rewarding ones. Interestingly, stimulant medication selectively remediated these abnormalities in ADHD, yet demonstrated a strikingly different effect profile in controls where it simultaneously heightened striatal RPE and SN/VTA novelty signals, reduced reward-learning rates and impaired overall performance. Preliminary cross-sectional evidence also suggests that long-term stimulant treatment is associated with a reduction in the rewarding value of novelty. Together, these results highlight a central role for aberrant novelty valuation in reward-related decision-making abnormalities observed in ADHD.

Previous modeling with simulated data has predicted that hypo-dopaminergic abnormalities will reduce learning rates and in turn account for key components of impulsive reward dysfunction in ADHD (Williams & Dayan 2005). By showing that ADHD patients exhibit reduced reward-related learning rates off medication, this work provides the first empirical evidence to support this. In addition, our data show a perturbation in the *acquisition* of reward-related behaviors in ADHD, supporting models that predict slower learning following positive reinforcement (Luman et al. 2010). This reduction in reward-learning rate may also underlie observations of reduced adaptability to changing reward schedules (Kollins et al. 1997) and increased temporal discounting (Williams & Dayan 2005) and help explain why reward-related learning deficits appear more pronounced when rewards are probabilistic or intermittent rather than continuous (Aase & Sagvolden 2006). Critically, our results also indicate that stimulant medication normalizes both learning rates and reinforcement-learning.

At first glance, the increased novelty and RPE signals we observed in ADHD may appear at odds with the hypo-dopaminergic profile believed to be central to this

disorder. However, this divergence is predicted by a number of accounts of ADHD which suggest that despite a reduction in tonic dopamine, phasic dopamine release is likely increased (Grace 2001; Seeman & Madras 2002; Cherkasova et al. 2014; Badgaiyan et al. 2015). Although it is not possible to directly address within the present fMRI study, these data show heightened error and novelty signals that are believed to be tightly linked to phasic dopamine. One possible mechanism underpinning this heightened phasic novelty profile is lower mesolimbic D2/D3 receptor density in ADHD (Volkow et al. 2009; Volkow et al. 2011). Functionally, a reduction in D2/D3 receptors would lead to disinhibited phasic dopamine release (Volkow et al. 2009; Volkow et al. 2011), potentially explaining the increased sensitivity to stimulus novelty we observe. Evidence to support this comes from molecular imaging studies of trait novelty-seeking in the healthy population, where lower D2/D3 (auto)receptor binding in SN/VTA is linked to higher novelty-seeking traits (Zald et al. 2008). The reduction of SN/VTA novelty signaling observed here after stimulant medication may equally reflect increased inhibition of these signals by D2/D3 activity, as methylphenidate exerts at least some of its therapeutic effects via increased dopamine binding to D2 receptors (Volkow et al. 2012). Indeed, stimulant-induced enhancement of tonic dopamine is predicted to preferentially activate D2/D3 receptors that inhibit phasic dopamine (Dreyer et al. 2010). Enhanced D2-mediated inhibition is consistent with the observation in ADHD of a more rapid decay in phasic response to novelty in response to stimulant medication despite no difference in the initial novelty signal (novelty valuation).

In contrast to the therapeutic effects observed in ADHD, methylphenidate impaired decision-making and learning rates and enhanced phasic RPE and novelty signaling in controls, to the extent they resembled un-medicated patients. These results are made more surprising by the fact that previous work has shown that in other, broader cognitive domains, methylphenidate has similar effects in both ADHD patients and controls (Agay et al. 2010). Thus, while stimulant medication appears to have equal impact on higher order cognitive functions in ADHD and controls (Agay et al. 2010), it appears to engender strikingly different effects on processes related to reinforcement-learning to reward. Reinforcement-learning abnormalities may therefore reflect a precise and disorder-specific therapeutic target for stimulant medication in ADHD. The fundamental origin of these differential effects remains unclear, though likely reflect baseline properties of the mesolimbic reward system. Indeed, while enhanced tonic dopamine and D2 activity may have a corrective role in ADHD and other hypo-

dopaminergic disorders such as Parkinson's Disease (Rutledge et al. 2009), increased D2 activity induced by methylphenidate in healthy controls (Volkow et al. 2001) may explain their poorer performance on drug. Correspondingly, selective D2 agonists appear to impair reward-learning in healthy subjects (Pizzagalli et al. 2008).

One possible explanation for the present findings is the difference in previous medication status. For instance, as ADHD participants were not taking there medication it is possible that their poorer un-medicated performance reflected a state of withdrawal rather than 'un-medicated' performance *per se*. To combat differences in medication status patients were asked to refrain from medication for 2 days prior to the session to ensure washout of the medication in line with prior research (Posner et al. 2011), and at least 4 times the half-life of available psychostimulant medications. However, the possibility of withdrawal effects on performance on the ADHD group cannot be fully ruled out and sufficiently long abstinence periods to ensure the absence of withdrawal effects may be considered to be ethically problematic. Future work with medication naïve patients may help to address this, however it is not possible to ensure that such individuals have appropriate therapeutic responses the study have an appropriately therapeutic response to a given medication or dose. As such, studies using medicated and medication-naïve individuals are both important to accurately assess baseline characteristics of ADHD and therapeutic effects of medication.

A further, preliminary finding from this study was an association between long-term stimulant treatment and a relative attenuation of both novelty valuation and SN/VTA responsiveness to novelty. The molecular mechanisms underpinning this potentially sustained improvement in novelty valuation are unclear. However, the current findings may link observations that markers of ventral striatal D2/D3 reactivity predict long term symptomatic improvements in attention (Volkow et al. 2012), and prior associations between SN/VTA D2/D3 receptor density and novelty-seeking behavior (Zald et al. 2008). Reductions in dopamine transporter (DAT) density after long term methylphenidate treatment are largely interpreted as effects of tolerance (Wang et al. 2013), yet a set of other neurobiological changes ascribed to methylphenidate use may also underpin potential long-term therapeutic benefits. These include increased neuroplasticity (Dommett et al. 2008), dendritic spine formation (Kim et al. 2009) and heightened expression of growth factors (Roeding et al. 2014; Simchon-Tenenbaum et al. 2015; Amiri et al. 2013) within limbic circuitry supporting novelty processing which

additionally contribute to long term therapeutic effects, independent of current stimulant medication status.

Further work is required to consolidate the broader clinical implications of the heightened novelty valuation observed here. For example, in addition to apparent roles in inattention and poor decision-making, heightened novelty valuation could well contribute to the high prevalence of substance use disorders observed in ADHD. Conversely, the apparent reduction in novelty valuation observed here with prolonged treatment, could underlie the reported reduction in substance abuse risks associated with long-term medication use (Wilens et al. 2003; Mannuzza et al. 2008). Longitudinal data is clearly required to investigate this hypothesis. To conclude, these findings suggest that novelty valuation has an important role in defining the ADHD phenotype and likely treatment response. Indeed, effects of methylphenidate on novelty processing revealed a remarkably disorder-specific effect not observed for other broader neuropsychological domains (Agay et al. 2010). Thus while some of the beneficial effects conferred by stimulant medication appear compensatory rather than corrective, actions on reinforcement-learning, and novelty processing in particular, appear to represent specific pathological targets.

6 General Discussion

This work employs recent methodological advancements to address several issues in the ADHD literature, focussing on the role of structures central to dopaminergic signalling. Various authors have questioned the importance of the brain dopamine system in ADHD. For instance, the putative absence of striatal volumetric abnormalities in adulthood has suggested that this region is not central to the persistence of symptoms (Nakao et al. 2011; Frodl & Skokauskas 2012). Chapter 3 shows that persistent striatal abnormalities are readily detectable in VBM analyses of adult ADHD when using MT saturation maps optimised for subcortical contrast. Furthermore, this chapter shows that previous T1-weighted VBM studies may have been insufficiently sensitive to detect these changes in adults. Chapter 4 provides evidence that altered microstructure of the primary dopaminergic nucleus in the brain, the SN/VTA, contributes to distinct forms of reward dysfunction considered to be central to ADHD. Specifically, incentive motivation and waiting impulsivity in ADHD appear to be linked to the microstructure of nigrostriatal and mesolimbic SN/VTA subcomponents respectively. Finally, Chapter 5 reveals that abnormal reward learning and decision making in ADHD is in part driven by aberrant novelty processing within the SN/VTA. Not only are these deficits rescued by dopaminergic medication in ADHD, but these therapeutic effects appear to be specific to ADHD individuals. Collectively, this work shows that application of appropriate methodological advancements reveals a clear picture of persistent abnormalities of the brain dopamine system in adult ADHD that are selectively targeted by short and long term stimulant medication use. The following chapter discusses the anatomical, functional, methodological and clinical implications of these findings.

6.1.1 Anatomical contributions of the dopamine system in ADHD

Previous findings have suggested that ongoing volumetric abnormalities within the striatum are not necessary for the persistence of ADHD into adulthood. However, it appears that this view may have been heavily influenced by the methodological approach these earlier studies adopted. The present work shows that striatal abnormalities are readily detected in an adult ADHD sample when using imaging contrasts specifically adapted to the challenges of subcortical imaging. By contrast, these striatal differences are not detected in exactly the same subjects when using T1-weighted volumes similar to those used in previous studies. These findings show that it

is necessary to be critically aware that structural imaging data does not offer a pure representation of brain morphology. Instead, T1 volumetry appears to be influenced by a range of other factors that are related to clinical and demographic variables of interest but do not actually represent changes in volume. This work shows that these confounding effects on analyses are not trivial – by using contrasts that exclude such confounds, a picture of persistent, rather than remittent, striatal abnormalities emerges.

By employing MT saturation maps in conjunction with diffusion tractography analysis, this work also highlights a role for the SN/VTA in ADHD. Moreover, whilst previous studies had shown that impulsivity (Buckholtz et al. 2010) and motivation (Volkow et al. 2011) were related to the dopaminergic midbrain, this work was able to functional localise these abnormalities to distinct subcomponents within the SN/VTA. Various models have posited the importance of describing how different functional abnormalities arise from distinct dopaminergic subregions (Castellanos et al. 2006). However, this work presents the first dissociation of neuropsychological differences in ADHD at the level of the SN/VTA.

6.1.2 Long term effects of stimulant medication on dopamine system anatomy

The methodological advancements employed by this thesis also offers an updated perspective on the long term structural effects of stimulant medication in ADHD. Contrary to previous findings this work does not detect any long term effects of medication on striatal volume, and points to the problematic nature of such inferences in previous studies. It is worth noting that the largest follow-up study of children with ADHD in adulthood also did not detect effects of medication on striatal volumes (Proal et al. 2011). Despite the potential confounds in previous reports, work in animal models does support the idea of long-term striatal alterations in response to medication (Kim et al. 2009). Well-controlled future MRI studies in humans using appropriate scanning protocols may be able to detect striatal volumetric changes.

In contrast to these striatal findings, the present study does find evidence for long-term changes in microstructural measures of the nigrostriatal, but not mesolimbic SN/VTA. Whilst longitudinal evidence is needed to confirm these findings, it appears that such changes may underpin long-term improvements in trait motivation in the disorder. Future studies are also required to examine precisely what underpins these changes in

microstructure. As previously noted, one possible explanation is stimulant-induced upregulation of growth factors (Roeding et al. 2014; Simchon-Tenenbaum et al. 2015) inducing multidirectional neurite development in this region (Rosenblad et al. 2000; Lin et al. 1993; Tomac et al. 1995; Hyman et al. 1991), however such an explanation remains purely speculative. Future work using models of diffusion that can assess neurite dispersion and density accurately in grey matter may provide some confirmation of this (Zhang et al. 2012). Additionally, future work will have to assess the apparent specificity of these long term microstructural changes to the nigrostriatal but not mesolimbic SN/VTA. Due to the high level of heterogeneity in pharmacological responses in these regions (Browder et al. 1981; Ashby et al. 2000; Goldstein & Litwin 1988; Gervais & Rouillard 2000; Mejías-Aponte et al. 2009; Mereu et al. 1987; Klink et al. 2001), numerous mechanisms could account for this. Further animal work will be required to disentangle how stimulant medication exerts these selective long-term effects.

6.2 Dopaminergic medication has disorder-specific effects in ADHD

First-line treatments of ADHD consist of dopamine-enhancing medications. The efficacy of these therapies has led to a theoretical focus on dopamine system abnormalities in ADHD. However, since then, the pathogenic and therapeutic importance of the dopamine system in ADHD has been called into question. This has been reinforced by studies suggesting that ADHD does not appear to be associated with dopamine abnormalities above and beyond poor attentional performance alone (del Campo et al. 2013), and that dopaminergic medication appears to enhance cognitive performance equally in the healthy population (Agay et al. 2010; Clatworthy et al. 2009). Paired with the observed heterogeneity of higher-order cognitive abnormalities in ADHD, such findings have led to some speculation as to its validity as a diagnostic construct. However, this thesis suggests that the neuropsychological non-specificity of ADHD appears to occur only in higher order cognitive functions. When examining specific functions that are tightly linked to dopaminergic function, a high degree of effects specifically associated with ADHD are observed.

6.2.1 Disorder specificity of medication in impulsivity and reinforcement learning

In both waiting impulsivity and reinforcement learning tasks employed here, stimulant medication appears to have effects that differ dramatically according to diagnosis. In the reinforcement learning task, stimulant medication has therapeutic effects of reward learning, novelty-directed behaviours, learning rates and novelty and error signals in ADHD, whilst the opposite effects are observed in controls. Although in waiting impulsivity, stimulant medication does not appear to confer therapeutic benefits in ADHD, it actually heightens waiting impulsivity in the healthy population.

These findings contrast starkly with observations that stimulant medication has comparable effects on higher-order cognitive functions in the healthy population (Agay et al. 2010; Clatworthy et al. 2009). This appears to show that the divergent effects of methylphenidate in ADHD and controls only occur in certain domains, and that these differential effects are most pronounced in impulsivity and learning and decision making (Dalley et al. 2007; Perry et al. 2008; Clatworthy et al. 2009; DeVito et al. 2008b; Campbell-Meiklejohn et al. 2012). Whilst it has been suggested that dopaminergic abnormalities are not central to ADHD (del Campo et al. 2013), these findings strongly suggest otherwise, as functions such as reward learning that are tightly tied to dopaminergic signalling show the greatest disorder-specificity in medication response. Whilst abnormalities in executive function may not therefore appear to have any level of specificity to ADHD, differences in dopaminergic function do appear to capture unique aspects of the ADHD phenotype and its responsiveness to therapy.

High levels of divergence in reward processing are also evident in the absence of pharmacological probes. For instance, whilst impulsivity in ADHD is associated with reduced activity in the ventral striatum during anticipation of reward, in healthy controls higher impulsivity is actually associated with greater ventral striatal anticipatory activity (Plichta & Scheres 2014). These findings collectively suggest the importance of dopaminergic abnormalities in defining ADHD pathogenesis, and highlight that different mechanisms appear to underlie impulsivity in ADHD and the general population.

These findings collectively indicate that ADHD diagnosis appears to have a profound impact on reward system function and its responsiveness to medication. The inverse nature of these effects in both groups appears to indicate that these individuals do not lie along a spectrum of heterogeneously poor performance, but appear to show distinct reward profiles according to diagnosis that are differentially modulated by dopaminergic interventions. By applying computational modelling methods, this work

also shows that it is possible to go beyond coarse descriptions of reward abnormalities and identify specific parameters contributing to them. Critically, it appears that these parameters share the same pattern of disorder-specific effects as reward learning performance. In particular, learning rates, prediction error signalling, and novelty processing all appear to show disorder-specific effects of psychostimulants. The following section attempts to integrate these findings with current models of dopamine dysfunction in ADHD.

6.3 Understanding the relationship between dopamine systems and abnormal reward function

Due to the development of more specific markers of reward dysfunction that are highlighted here, it has become increasingly possible to integrate observed reward abnormalities in ADHD with theories of abnormal mesolimbic dopamine function. As previously discussed, various theories of ADHD pathophysiology differ in their appraisal of altered dopaminergic function in ADHD. Whilst a general hypodopaminergic deficit has been postulated (Volkow et al. 2005; Sagvolden et al. 2005), other accounts have suggested that reduced tonic but heightened phasic dopamine is observed (Grace 2001; Seeman & Madras 2002; Badgaiyan et al. 2015). By modelling error and novelty signals that reflect phasic dopamine release (Schultz & Dickinson 2000), the present data is able to contribute to this debate. Specifically, the increased error and novelty signals that are observed in ADHD supports models that predict a hyper-phasic signalling profile. Moreover, this data suggests that heightened phasic dopamine signals are reduced by stimulant medication, likely via enhanced D2-mediated inhibition of phasic dopamine as previously discussed (Dreyer et al. 2010; Seeman & Madras 1998). Recent PET studies also appear to support this low-tonic, high-phasic dopamine theory of ADHD (Badgaiyan et al. 2015). Interesting, such a model of dopamine pathophysiology would also predict other neuropsychological components of ADHD. For instance, as incentive motivation is linked to tonic dopamine levels (Niv et al. 2007), reduced motivation in ADHD would actually be predicted by a model suggesting low tonic dopamine in the disorder.

Linking other abnormalities in ADHD to such a model is more challenging however. For instance, this work reveals low learning rates in ADHD. Learning rates are frequently taken to represent dopamine levels (Williams & Dayan 2005), though a more precise

neurobiological interpretation is lacking. It is tempting to ascribe a linear relationship between tonic dopamine levels and learning rates, though such an analysis does not appear to hold. Whilst enhancing synaptic dopamine levels by administration of methylphenidate appears to increase learning rates in ADHD, precisely the opposite relationship is found in controls. This appears to suggest a more complex relationship of learning rates to tonic dopamine levels. One possibility is an inverted-U shaped relationship between tonic dopamine and learning rates. In this instance, enhancement of tonic dopamine levels in ADHD and other hypodopaminergic disorders would increase learning rates, whilst increasing already optimal tonic dopamine above this threshold would reduce them. Such a model would however struggle to explain how high learning rates could be described in terms of tonic dopamine levels alone. Another, perhaps more plausible model may describe variation in learning rates in relation to a balance between phasic and tonic dopamine levels. However, such possibilities remain purely speculative, as no work to date has attempted to clarify the precise relationship between brain dopamine and learning rates.

Another area in need of clarification is the relationship of waiting impulsivity to dopaminergic and/or noradrenergic abnormalities in ADHD. This work shows that abnormal waiting impulsivity is related to abnormal microstructure of the mesolimbic SN/VTA. This is consonant with findings that the nucleus accumbens, one of the key regulatory targets of the mesolimbic SN/VTA, also has a central role in waiting impulsivity (Economidou et al. 2012). However, as previously noted, methylphenidate appears to exert its effects through opponent processes mediated by dopaminergic and noradrenergic signalling in the nucleus accumbens core and shell respectively (Economidou et al. 2012). In ADHD, the dopaminergic effects of methylphenidate on waiting impulsivity appear to be altered or less pronounced, somewhat counter-intuitively inhibiting the impulsivity enhancing effects of this drug that is observed in controls (Voon et al. 2015). Future work must therefore carefully examine the interactions between dopaminergic and noradrenergic signalling in the core and shell of the accumbens, and assess how this is modulated by the mesolimbic SN/VTA.

6.4 Future methodological considerations

This work highlights the importance of employing advancements in MR and neuropsychological methodologies in refining pathological and therapeutic

mechanisms in ADHD. The following sections will review these approaches and how they may be further applied within ADHD, but also more broadly to other problems.

6.4.1 Improving structural investigations and analyses

Firstly, this work shows that the employment of alternate structural imaging methods has an appreciable impact on results. In the case presented here, recognising the limitations of T1 imaging of subcortical structures and adjusting protocols accordingly has the capacity to resolve previous inconsistencies in the literature regarding striatal morphometry in adult ADHD. Similarly, this work highlights the utility of MT saturation maps in imaging the SN/VTA which is not visible in typical T1 weighted volumes. This heightened contrast not just in ADHD, but also other disorders with hypothesised subcortical components. Importantly, this also highlights the necessity of adopting such methodologies in any maturational studies (Martin et al. 1998), where iron content associated with age may bias volumetric investigations. This is also essential when investigating disorders of the dopamine system, due to the relationship between brain iron and dopamine (Youdim et al. 1983; Bianco et al. 2008). Apparent volumetric differences, or their absence, that are associated with age or dopaminergic disorders could therefore be biased by iron differences linked to these conditions. These findings highlight the potential of these pitfalls, with implications for morphometric analyses of the brain in various conditions.

Secondly, this work shows that using diffusion MRI tractography to parcellate structures of interest can greatly enhance specificity of structural investigations. Using these techniques it is possible to functionally localise abnormalities to different substructures. In this case, impulsivity and motivational abnormalities have both been previously ascribed to the SN/VTA, and using parcellation methods it is possible to localise these differences to the mesolimbic and nigrostriatal SN/VTA respectively. In addition to refining description of functional-anatomical relationships in ADHD, these findings also have possible implications for therapy, as long-term stimulant treatment only appears to affect one of these components, and only those functions ascribed to it. Employing microstructural measures may also provide a more sensitive measure of long-term changes, as these data reveal long-term effects of medication on SN/VTA subcomponent microstructure but not volume.

This work also uses a novel up-sampling technique that allows for higher-resolution parcellation analyses of smaller structures without altering acquisition. This intends to

improve parcellation results in the boundaries between subregions within small structures, particularly in winner-takes-all strategies. A slightly higher probability of connection to one target than another in a single voxel will result in the same binary identity being assigned as a much larger difference between these two targets. In small structures where a single such boundary voxel makes a relatively large contribution this is particularly problematic. The current up-sampling approach allows for a potentially smoother parcellation within these small structures, allowing for the gradient region between subregions to be parcellated at a finer scale. It must be noted however, that this upsampling is only in effect smoothing the data to reduce variance and is not offering novel information at this higher resolution. Parcellating small structures with more than two subregions, where a single gradient cannot be assumed, may therefore be problematic. For instance, the periaqeductal grey (PAG) contains several subdivisions along both rostral-caudal and superior-inferior dimensions (Coulombe et al. 2016), and interpolation may interfere with identifying these accurately.

6.4.2 Improving modelling of reward and medication

Finally, this thesis also shows the importance of computationally refining neuropsychological constructs. Reward abnormalities in ADHD have been frequently observed, but by applying computational models this work demonstrates that it is possible to isolate specific pathological mechanisms, and show how these are altered by medication. Going forward, this will be essential to further clarify the nature of abnormalities in ADHD. This will, for instance be essential in highlighting the nature of motivational abnormalities in ADHD beyond the coarse concept treated here.

In contrast to the work studying reinforcement learning in this thesis, the measures of incentive motivation are relatively course. This work employs indices of trait motivation that afford ease of comparison to previous studies in ADHD (Volkow et al. 2011). However, by using trait measures it is not possible to measure acute responses to medication. Moreover, motivation is not a unitary function and future work is necessary to refine how differences in intrinsic and extrinsic motivation contribute to ADHD. Whilst the majority of motivation research has focussed on extrinsic motivation that is, put simply, the extent to which behaviour and effort is motivated by reward, no work has examined how intrinsic motivation (ie motivation to engage in behaviours that are not

externally rewarded) is altered in ADHD. Future work may be able to model these intrinsic factors in reinforcement learning paradigms (Barto 2013). Similarly, the motivation to perform an action for reward is also modulated by a variety of factors, such as satiety, boredom, appetitive states. Modelling the contribution of these factors is in its relative infancy (Berridge 2012), but critical for further clarifying reward and motivational processes in ADHD. This is highly relevant, as motivated behaviours are not uniformly impacted in ADHD. For instance, inattention and response inhibition deficits are completely normalised when more game-like representations of typical neuropsychological tests are used (Bioulac et al. 2014; Shaw et al. 2005). Computational modelling may help to quantify these altered motivational states, assess how they are neurobiologically instantiated, and start to investigate how they might be best maintained during tasks that individuals with ADHD find challenging.

6.4.3 Study limitations

A more general methodological concern in the present work is the high depression and anxiety scores. However, ADHD is strongly associated with depressive and anxious symptoms. The prevalence of depression specifically is at around 19% in adults with ADHD, compared to approximately 8% in individuals without (Kessler et al. 2006). Even in the absence of clinically significant scores, many ADHD participants exhibited higher levels of depressive symptoms than controls. It is unlikely these effects account for the results reported however. The majority of results reported survive correction for BDI and STAI scores, and outcome measures that were reduced to trendwise significance after correction were not associated with either depression or anxiety levels.

One final issue that could influence the interpretation of the current studies is the difference in medication exposure between the two groups of participants. ADHD patients had all been taking regular doses of stimulant medication to ensure clinical efficacy, but control participants had never taken these drugs. This set up was also required to allow for cross-sectional investigation of the neurobiological correlates of long-term medication. This could however have affected acute responses to these medications. To minimize this risk, patients were medication abstinent for two days before each experimental session. Interpretation of the acute effects of medication in these groups must however take this into consideration. It does however appear

unlikely differences in medication exposure could account for these results. In particular, the strikingly different patterns of effect that are observed in reinforcement learning and novelty signalling appear unlikely to be the result of any effects of tolerance. Although it appears initially more plausible that the lack of effects of medication on waiting impulsivity in ADHD compared to controls could reflect tolerance, this also appears unlikely as animal models without drug pre-exposure show similar results (Paterson et al. 2011).

6.5 Clinical implications

Clinically these findings provide a mixed picture of the efficacy of dopaminergic medication in ADHD. Stimulant drugs appear to normalise reward learning and novelty processing, highlighting their importance in treating abnormalities directly related to dopaminergic systems in ADHD. In addition to these acute effects however, this work suggest that stimulant drugs may have long-term therapeutic effects on reward and motivational abnormalities. If such observations are replicated, future clinical work will be necessary to examine whether such normalisations persist following prolonged periods of abstinence. Evidence has suggested that childhood treatment of ADHD is associated with reduced propensity to substance abuse (Mannuzza et al. 2003) and higher likelihood of adult employment even after controlling for current treatment status (Halmøy et al. 2009). These findings highlight the critical importance of early treatment in long-term outcome. The long-term changes in novelty processing and motivational systems that are observed may underpin such changes in childhood. However, the current studies also suggest that such long-term changes may also be observable in treatment of adults ADHD. Whilst it is clear that early intervention is paramount for long term outcome, these findings may also suggest a more optimistic outlook in the remittance of ADHD symptoms and improved outcome even in adulthood. Future work monitoring long-term treatment effects in patients diagnosed in adulthood will be necessary to add to this clinical picture, and open up the possibilities of examining the requirement of lifelong medication regimes in patients who show stable long-term responses.

Although this work highlights the efficacy of dopaminergic medications in reward abnormalities, their lack of efficacy in treating waiting impulsivity deficits highlights the importance of reviewing current therapies based on symptom profiles. Indeed, current

evidence suggests that atomoxetine may have greater success in treating impulsive symptoms. Future studies must closely examine the effects of dopamine and noradrenaline acting drugs in treating combined, predominantly hyperactive and predominantly inattentive subtypes of ADHD. Whilst the presence of ADHD subtypes has long been diagnostically recognised, this is currently not a primary consideration when opting for dopaminergic therapy. If future work confirms the efficacy of atomoxetine in treating waiting impulsivity, altering this approach will be necessary, as the present study suggests that stimulant medication may lack any therapeutic effect in treating primarily hyperactive and impulsive subtypes.

Developing such approaches may also be important for future drug development. Chapter 4 suggests that ADHD pathophysiology occurs within both mesolimbic and nigrostriatal SN/VTA, however data from this chapter also indicates that the nigrostriatal rather than mesolimbic SN/VTA appears to be therapeutically targeted by current psychostimulant medications. For instance, waiting impulsivity which appears to be underpinned by the mesolimbic SN/VTA, does not seem to be behaviourally affected by acute medicate in ADHD. Moreover, Chapter 4 presents preliminary evidence that long term exposure appears to be related to the microstructure of the nigrostriatal but not mesolimbic SN/VTA. Due to the extensive differences in pharmacological profile in this region, it is difficult to speculate precisely why current psychostimulants affect only the nigrostriatal but not mesolimbic SN/VTA therapeutically. Though future work will be required to determine if this is indeed the case, this model would predict that drugs with selective therapeutic effects on the mesolimbic SN/VTA may be important for preferentially treating impulsivity in ADHD. In instances of combined type ADHD future drugs targeting both subsystems may be required, as current treatments appear to have selective therapeutic effects on the nigrostriatal SN/VTA.

Owing to the ostensibly similar cognitive benefits of methylphenidate in the healthy population (Agay et al. 2010), a growing interest has developed in the use of methylphenidate as a cognitive-enhancing substance (Sahakian & Morein-Zamir 2015). Whilst the beneficial effects of methylphenidate may be shared by the general population in some domains, this work highlights highly detrimental effects of the drug in reward learning and impulsivity. The use of methylphenidate as a cognitive-enhancer should therefore be treated with some degree of caution. Due to these stark differences of effect in ADHD and controls that are observed here, the long-term safety

and tolerability profile of these drugs that is observed in ADHD may not be transferrable to the general population.

6.6 Future studies

In addition to the suggested future directions described above, several potential studies that follow near directly from questions raised by this work should be highlighted. Firstly, much of the discussion of the results from Chapter 5 has suggested that novelty processing in ADHD is linked to enhanced phasic novelty signalling, and that increased D2 mediated inhibition of these phasic signals may explain the reduction of novelty signalling we observe in response to medication (See Chapter 5 discussion and above within this chapter). Future dual tracer PET studies will be important to test this directly. In particular, assessing the binding potentials of D1 and D2 receptors with radiolabelled ligands will help assess the hypothesis that reduced novelty signalling reflects a relative increase in activity of the inhibitory D2 receptors to D1. Whether this can be applied specifically to novelty processing is a challenge however, as the paradigm utilised here requires a temporal resolution greater than that offered by PET imaging. A block design task using novel and familiar images on and off medication may allow the assessment of D1/D2 binding during novelty processing, though it would be difficult envisage how such a task would work within a reinforcement learning framework. Alternatively D1/D2 binding ratios could be related to behavioural changes detected in data collected prior/post scanning.

Another pressing future study is a longitudinal examination of ADHD neurobiology using MT saturation VBM. Although we find no evidence of long term structural therapeutic changes in the striatum using MT saturation VBM, we also cannot rule out the possibility in this cross-sectional study. Whilst this work uses subcortically optimised structural imaging to detect differences in adults in ADHD that have been argued to remit, this does not rule out the possibility of some effects of treatment and maturation. Similarly, the long term effects of medication in both Chapters 4 and 5 we do observe must be validated with longitudinal designs. Though such studies are challenging, they are essential to accurately infer therapeutic and maturational effects in ADHD.

6.7 Conclusions

Overall, these findings highlight the ongoing relevance of the anatomy and function of mesolimbic and nigrostriatal systems in ADHD. These networks appear to underpin key neuropsychological abnormalities in the disorder that are targeted by dopaminergic medications in a disorder-specific manner. Moreover, this thesis presents preliminary, cross-sectional evidence for therapeutic structural and functions alterations in response to these medications. However, it is also clear that ADHD is also associated with a range of abnormalities in higher order functions and the networks underpinning them. A developing idea is that these higher order deficits are underpinned by differences in core dopaminergic functions. Not only are higher-order networks modulated by dopaminergic nuclei (Cole et al. 2013), but the functions they subserve can be therapeutically targeted by both dopaminergic medication and naturalistically altering the rewarding and motivationally salient properties of tasks (Liddle et al. 2011). It appears likely then, that mesolimbic and nigrostriatal differences in reward and motivation may explain such higher order deficits. This work takes steps to refining the current understanding of structural and functional abnormalities in motivational and reward networks that may underpin this. Future work will be required to further refine abnormal dopaminergic function in ADHD, and determine how it relates to the higher order deficits that have long been used to define the disorder.

7 References

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